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FURTHER STUDIES OF THE MECHANISM OF PULMONARY CLEARANCE OF PRODIGIOSIN IN NORMAL AND X-IRRADIATED RABBITS

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IN PREVIOUS studies,[25] it has been shown that the respiratory tract of rabbits clears itself rapidly of inhaled insoluble particles. Furthermore, wholebody x-irradiation appears to accelerate the rate and increase the efficiency of the normal clearance mechanisms involved.[24] However, these inhalation studies did not provide specific data by which an evaluation of the separate mechanisms could be made. Therefore, similar serial sacrifice experiments were repeated, administering colloidal prodigiosin to normal and to x-irradiated rabbits by intravenous injection.

In this manner a qualitative evaluation of the role played by phagocytic function as distinct from the other major mechanisms of lung clearance, namely, ciliary action and mucus secretion, was made possible. In addition, data on the relationship between spleen weight and mortality rates during the acute phase (first thirty days) of the radiation syndrome have been accumulated and correlated with changes in prodigiosin blood retention following intravenous injection of the dye. An inverse relationship exists between dye retention and spleen weights. Mortality rate is highest shortly after spleen size shrinks to its minimum and during the period of maximum prodigiosin blood retention.

Two other related studies were made to help evaluate the phagocytic

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factor in lung clearance. Prodigiosin uptake in the spleens of normal and x-irradiated animals was determined following inhalation exposure and at the same intervals after intravenous injection of the colloidal dye.

The findings of all these experiments now begin to show significant interrelated patterns which help to provide a better understanding of the phagocytic factor in normal lung clearance mechanisms. Also it appears that the temporary depression of phagocytic function of the reticulo-endothelial system, following penetrating radiation exposure, may be involved in radiation deaths from bacterial causes. Most important in respect to the inhalation hazard in atomic warfare and to dust hazards in industry, these animal studies suggest that normal pulmonary defense mechanisms provide the body with a large safety factor which is even more effective in the event of concurrent whole body radiation injury.

EXPERIMENTAL

Procedures and Equipment.—Dutch rabbits weighing 1.5-2.0 kilograms were used throughout this study. The animals were given 800 r whole body roentgen ray irradiation using a 250 kvp Picker Industrial Unit. The technical factors were: 250 kv; 15 ma, tsd 100 cm; filters, 0.21 mm Cu inherent, 0.50 mm Cu parabolic and 1.0 mm al; hvl 1.93 mm Cu; size of field—total body; r/minute measured in air, 10. The 250 kvp Picker Industrial unit used was calibrated before each experiment with a Victoreen Thimble r meter.

Preparation and Standardization of Prodigiosin Used.— Crystalline prodigiosin base* was mixed with powdered dextrose and ascorbic acid in the following proportions: prodigiosin base, 0.1 gm. ascorbic acid, 0.5 gm., and dextrose, 5.0 gm. Multiple quantities of the mixture were mixed and ground with sufficient 5.0 per cent dextrose and 0.5 per cent ascorbic acid in distilled water to form a polydispersed colloid containing approximately 2 mg prodigiosin per ml. This colloidal suspension of large particle size was then centrifuged for forty-five minutes at 10,000 rpm (Spinco) and the supernatant was used for injection. The resulting suspension was standardized for prodigiosin concentration and stored at 5° C. in a light-protected bottle. In order to correct a slight but gradual fall in concentration, the prodigiosin content of the final preparation was redetermined at weekly intervals throughout this study.

Methods of Prodigiosin Measurement and Tissue Extraction.—Lungs and spleens were removed, weighed and minced. Prodigiosin was extracted from tissue specimens with acid chloroform by using a Waring Blendor. Blood plasma specimens were extracted with alkaline petroleum ether.

*Prodigiosin base used in these studies was obtained from Dr. Arthur Lack, formerly of Birmingham Veterans Administration Hospital, Van Nuys, California.

The details of the extraction procedures and of the spectrophotometric method of analysis have been reported previously.[23]

Dosage of Colloidal Prodigiosin.—All animals were weighed just prior to dye administration. The standard dosage of dye employed in all except the distribution studies was 1.3 mg/kg, using a dye concentration of approximately 1.0 mg/ml. Recovery was determined on the basis of μg prodigiosin per gram of wet tissue.

Procedure of Blood Clearance.—The procedure used to measure prodigiosin retention in the blood was to obtain a 5-10 ml sample of blood by cardiac puncture five minutes after intravenous injection of the standard dose of dye. This interval was selected after plotting the normal clearance curves from data obtained on a large series of rabbits wherein blood samples were drawn one, three, five, ten and fifteen minutes post injection. This single sample technique was used because it does not disturb the circulatory dynamics. Furthermore, the procedure gave reproducible results.

RESULTS

It has been shown (Table I) that after intravenous injection of 1.0 mg/kg of colloidal prodigiosin, the dye is rapidly distributed throughout the organs of the reticuloendothelial system. The dye was not excreted in the urine. In Figure 1 the relationships between prodigiosin blood retention, spleen weight and mortality are shown in graphic form, demonstrating the inverse relationship between spleen weights and blood retention throughout the first thirty days post-irradiation. It is stressed that there is an important time factor involved. When the spleen weights shrink to a minimum (three to eight days), blood retention reaches its peak levels. As the spleen returns to normal size (fifteen to thirty days) blood retention falls to or below the ranges of concentration noted among non-irradited controls. It is possible that the correlation between mortality rate and this evidence of temporarily depressed phagocytic function has significance regarding the bacterial factors involved in mortality from radiation injury.[17,18]

Pulmonary Clearance of Prodigiosin Administered by Inhalation Compared with Intravenous Injection.—Inspection of data presented in Figure 2 shows the effect of the route of administration on the removal of prodigiosin from the lungs of normal and x-irradiated rabbits. With the inhalation route, all protective mechanisms are concerned, namely, ciliary action, increased mucous secretion and phagocytosis; whereas in animals given the dye by injection, none of the dye reaches the tracheobronchial passages and phagocytosis is the primary mechanism of removal. Data from the

TABLE I. DISTRIBUTION OF COLLOIDAL PRODIGIOSIN IN ORGANS OF THE RETICULO-ENDOTHELIAL SYSTEM OF NORMAL RABBITS AFTER INTRAVENOUS INJECTION

Micrograms of Prodigiosin Recovered 15 Minutes after Injection

Animal Weight Kg.	Dosage micro-gram	Lung		Liver		Kidney		Spleen		Bone Marrow		Brain		Total 1st Ext.	Recovery 1st Ext. + 20%	Percent Recovery
		per gram	per organ	per gram	per organ	per gram	per organ	per gram	per organ	per gram	per organ	per gram	per organ			
1.60	1600	7.9	66.0	1.8	100.0	3.8	21.3	2.2	1.1	2.8	41.7	3.8	2.9	233.0	279.6	18.7
1.60	1600	16.8	100.8	3.1	125.0	3.8	19.0	7.4	5.2	1.9	28.4	0.96	8.0	286.4	343.8	21.6
1.50	1500	24.9	148.2	2.5	136.0	2.9	19.9	5.5	2.7	2.7	41.1	0.99	6.5	354.4	422.1	28.8
1.60	1600	12.9	77.4	2.1	93.5	3.2	23.5	6.9	6.4	1.9	27.8	1.2	8.0	236.6	284.0	17.8
1.30	1300	22.8	115.1	1.8	70.5	3.6	15.3	5.1	2.0	2.3	34.8	1.2	7.8	245.6	294.7	22.7
1.90	1900	14.9	93.0	3.6	220.0	7.0	48.0	15.4	8.4	3.9	58.8	2.7	20.0	448.2	538.1	23.6
Average Values																
1.58	1583.3	16.7	100.1	2.5	124.2	4.0	24.5	7.1	4.3	2.6	38.8	1.8	8.9	300.7	360.4	22.2

Notes: 1. Prodigiosin Dosage, 1000 micrograms per kilogram body weight.
2. Concentrations of Prodigiosin Suspension, 800 micrograms per milliliter.
3. Total Weight of Bone Marrow estimated at approximately 15 grams.
4. Percent recovery corrected upward by 20% to account for the amount of prodigiosin retained after a single extraction procedure.

inhalation series (A) show that the lungs of irradiated animals are cleared much more rapidly and completely than those of non-irradiated controls. Furthermore, both the rate and degree of removal are decidedly greater in both irradiated and non-irradiated animals in the inhalation series (A)

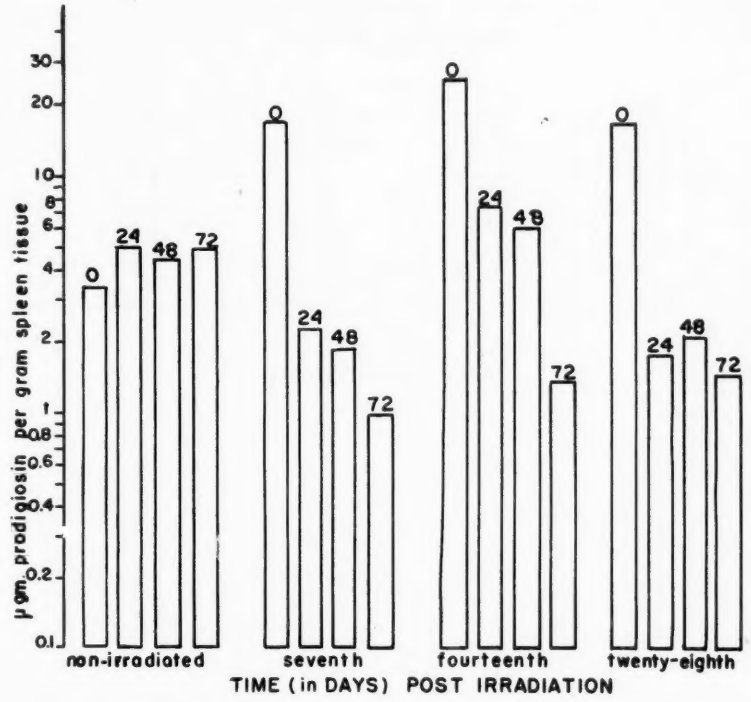

Fig. 1. Relation Between Mortality Rates, Spleen Size, and Blood Retention of Prodigiosin in Normal and X-Irradiated Rabbits.
Note: Data shown were obtained from sacrifice studies using a total of 310 animals.

compared with the series (B) given the dye by intravenous injection. A direct quantitative comparison of one series with the other is not possible because of the unavoidable difference in amounts of dye initially deposited in the lungs following injection versus dust exposure.

Athough the clearance of injected colloidal prodigiosin (Series B) is slightly more complete in the irradiated groups than in their controls, indicating a possibly stimulating effect of radiation on phagocytosis, the differences are much less striking than those seen in the inhalation series (A) wherein the major mechanisms appear to be either increased ciliary activity or mucus secretion. Therefore, it appears that in normal rabbits phagocytosis is less important as a pulmonary defense mechanism than is ciliary

activity and/or mucous secretion. Following x-irradiation, all defense mechanisms are more effective, particularly ciliary action and/or mucus secretion. The phagocytic factor is likewise more effective, especially during the third and fourth weeks post-irradiation.

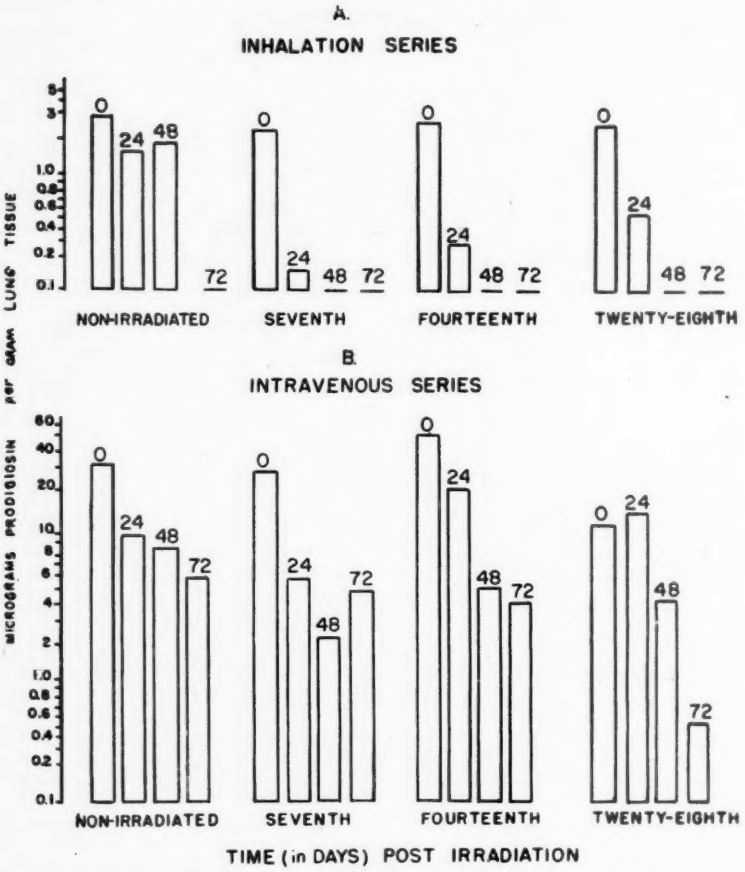

Fig. 2. Effect of the Route of Administration of Prodigiosin on its Removal from the Lungs of Normal and X-Irradiated Rabbits.

Notes: 1. Numbers over bars indicate time (in hours) of sacrifice after dosage of Prodigiosin.

2. Each bar in the graphs represents the mean value computed from determinations on six animals.

An Indirect Estimate of Phagocytic Function as Altered by Whole Body Exposure to X-irradiation.—Following single thirty-minute inhalation exposures of rabbits to prodigiosin dust by techniques previously described,[23] spleens were removed at specific intervals from both normal and x-irra-

diated animals and their prodigiosin content was determined. It was believed that data obtained in this manner might contribute to a better understanding of the phagocytic aspects of the problem of lung clearance. It was realized that the spleen is a small but nonetheless important part of

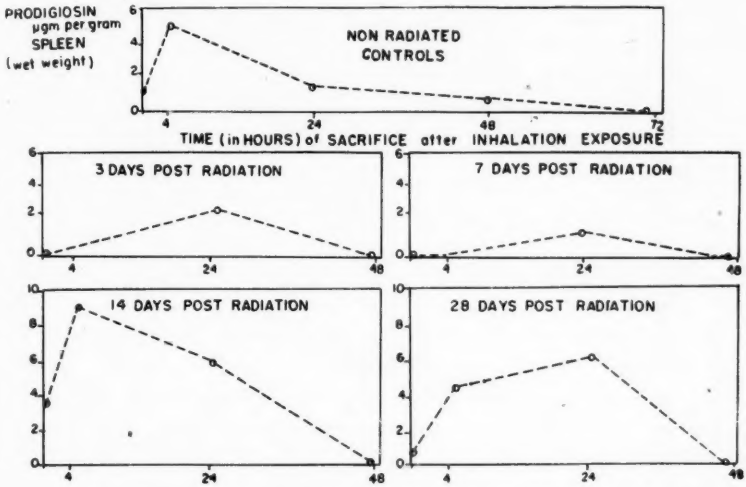

Fig. 3. Prodigiosin Content in Spleens of Normal and X-Irradiated Rabbits (800 r LD 50) An Estimate of Phagocytic Function.
Note: Each value shown in all curves represents the mean from determinations on six separate animals.

the entire reticuloendothelial system, and that quantitative evaluation of phagocytic function in this single organ may not reflect the activity in other parts of the system. Nevertheless, the results shown in Figure 3 provide an indirect index of phagocytic function of the lung macrophages. These cells are the means of transport for inhaled dust particles from the lungs to the spleen via the pulmonary lymphatics and the general circulation The line graphs in Figure 3 show, first, that spleens of normal rabbits begin to contain measurable amounts of prodigiosin immediately (within fifteen minutes) and peak concentrations are reached at around four hours. By seventy-two hours the spleens gradually become cleared of dye. This curve for normal animals differs from others plotted from data on animals exposed to 800 r whole body x-irradiation and tested in a similar manner at three, seven, fourteen and twenty-eight days post-irradiation. At the third and seventh post-irradiation days, the four-hour dye content is generally lower than in non-irradiated controls, and peak levels are not reached until about twenty-four hours. However, the spleen is cleared within forty-eight hours; whereas in non-irradiated animals complete clearance is not reached until about seventy-two hours. In the series

studied at the fourteenth day, peak concentrations occur at about four hours but clearance is more rapid than in the controls. Even on the twenty-eighth day the rate of dye turnover is still more rapid than in non-irradiated animals.

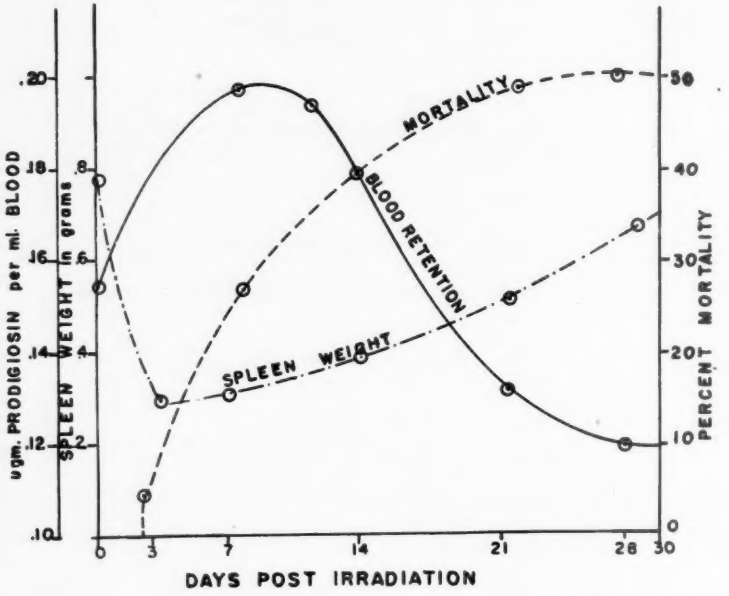

Fig. 4. Splenic Uptake of Injected Prodigiosin in Normal and X-Irradiated Rabbits. Notes: 1. Numbers over bars indicate time of sacrifice (in hours) after each intravenous injection of colloidal prodigiosin.
2. Each bar in the graphs represents the mean value computed from determinations on six animals.

Splenic Uptake of Intravenously Injected Colloidal Prodigiosin as Altered by Whole Body X-irradiation.—Data presented in Figure 4 show that the initial uptake of prodigiosin per gram of spleen is greater in irradiated animals at specified times during the acute post-irradiation period than in the non-irradiated controls. Also, the rate and completeness of dye clearance from the spleen is greater in irradiated versus non-irradiated controls. These findings present a paradox, since one would expect increased splenic uptake to be accompanied by decreased dye retention in the blood. The resolution of this problem must await accumulation of additional data. Some of the probable determining factors are variations in phagocytic activity, redistribution of dye particles from one organ to another with passage of time, and unknown effects of ionizing radiation on handling of dye particles after they have been engulfed by the macrophages.

DISCUSSION

General Significance of Results.—Comparison of lung clearance data between groups of rabbits administered colloidal prodigiosin by inhalation and by intravenous injection has demonstrated clearly that phagocytosis is a less important defense mechanism than ciliary action and/or increased mucus secretion in both non-irradiated animals and animals previously given 800 r exposures of whole body x-irradiation. This basic information may be useful in evaluating the inhalation hazards in atomic warfare,[4,10] industry,[2,6,11,12] allergic diseases,[1,21,22,26] and in consideration of the rationale for radiation therapy in certain clinical disorders of the respiratory tract.[3,15,16,19] The major practical importance of these findings is the knowledge that the normal mechanisms, which defend the lungs from inhaled insoluble foreign particles, are highly effective and provide the body with a considerable physiological safety factor. More surprising is the evidence which indicates that radiation exposure enhances both ciliary action and phagocytic function in respect to protection of the pulmonary tree from insoluble, finely divided, particulate foreign material.

Analysis of Prodigiosin Blood Retention Data.—The information regarding blood retention of intravenously injected colloidal prodigiosin is a small part of the total data so far accumulated on this phase of the problem. A more complete presentation of the effect of whole body radiation exposure on blood prodigiosin retention is in preparation. The data herein presented is given because it is another index of the action of whole body irradiation on phagocytic function of the reticuloendothelial system in general and in respect to pulmonary clearance of this dye in particular. From data shown in Figure 1 it is apparent that 800 r whole body x-irradiation in rabbits increases blood retention of the dye for about fifteen days post-irradiation and decreases it below normal during the sixteenth to twenty-eighth days. These findings are interpreted to mean that an LD_{50} dose of x-irradiation initially depresses phagocytic function of the reticuloendothelial system and this action is followed by an undetermined period of functional overactivity. Available information which has not been included in this open report has shown that with the 800 r doses of radiation, the increase in blood retention appears to be nearly completely caused by alteration in phagocytic function of reticuloendothelial cells (macrophages) and not to the circulating leukocytes. This interpretation is based on the observation that although 300 r of whole body x-irradiation is sufficient to produce neutropenia,[9] it is not enough to disturb the efficiency of prodigiosin blood clearance in rabbits. Furthermore, 1200 r doses given in the same manner are followed by even more striking increases in blood retention than those found after 800 r exposures.

Although rabbits were selected for this study because of the similarity between their respiratory organs and those of man, the conclusions drawn

cannot be applied indiscriminately to man or other animals because of the unpredictable variations in response to whole body irradiation, even within one animal species.[14] However, these studies do shed light on the physiological mechanisms by which one species of mammals protects itself from inhaled insoluble particulate material, and demonstrates the striking efficiency of these defenses, especially under such adverse and damaging influences as serious exposure to whole body ionizing radiation.

In conclusion, it would seem plausible that if the depressed phagocytic functions of the relatively radioresistant reticuloendothelial cells were stimulated by agents applicable in clinical medicine, such stimulation during the acute phase of the radiation syndrome[20] might reduce the incidence of sepsis and deaths from the bacterial complications which persist after antibiotic therapy.[5,7,8,13]

SUMMARY

In rabbits 800 r of whole body x-irradiation appears to accelerate the rate and increase the efficiency of the major mechanisms by which the lungs clear themselves of insoluble foreign particles following acute inhalation exposure. Ciliary action and/or increased mucus secretion play a greater role than phagocytosis. Both mechanisms are more effective in x-irradiated animals than in non-irradiated controls. Indirect indices of phagocytic function of the reticuloendothelial system, such as spleen weight, colloidal dye retention in the blood and splenic uptake of inhaled insoluble prodigiosin dust, indicate that LD_{50} doses or larger of whole body x-irradiation produce an initial depression (nothing to fourteen days) of phagocytic function among the relatively resistant macrophages. Peak mortality rates occur during this same time interval, whereas in the succeeding two weeks, death rates decrease sharply. During this latter interval, spleen weight increases rapidly and is associated with a physiological rebound in respect to phagocytic function in the reticuloendothelial system. The possible clinical significance of the effectiveness of normal lung clearance mechanisms is discussed with respect to the inhalation hazards in atomic warfare, and in both industrial and clinical medicine. The findings also suggest that pharmacologic stimulation of functionally depressed reticuloendothelial cells during the acute phase of the radiation syndrome might be beneficial in conjunction with antibiotic therapy in reducing the mortality from bacterial causes.

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THE IMPORTANCE OF THE SPECIFIC ALLERGEN

A Case Report

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E. McG., a white boy seventeen years old but in appearance no more than twelve or thirteen years, thin, sickly, pale, undernourished and underdeveloped, with an ichthyotic skin, had suffered from bronchial asthma since the age of five and a half. The first attack occurred during the winter. The cause could not be ascertained. It was not, however, preceded by nasal or other respiratory infection. His asthmatic attacks, at first mild and infrequent, increased in both frequency and severity as time went on, to an extent that wheezing and dyspnea were almost constant and frequent hospitalization and the use of oxygen, intravenous glucose, and aminophylline became necessary. These severe attacks usually left him in a weakened condition. Though he was always on an adequate diet, his growth was stunted and he could not gain weight.

The markedly ichthyotic skin made it impossible to test him directly, and passive transfer was resorted to. Slight reactions were obtained to the following: feathers, dust, tobacco, rabbit epidermis, timothy, silk, chicken, and cornmeal.

The positive inhalants, contactants, and foods, as well as such offenders as fish, nuts, and chocolate, were eliminated. Nonspecific treatment with stock dust and vaccine was given. Various medications including iodides, aminophylline, Tedral, antihistamines, vitamins, and so forth, were administered, with very little relief of symptoms or effect on his general nutrition. Large doses of vitamin A had no influence on his skin condition, and this was discontinued.

Questioning about a possible cause of the asthma attacks was carried on at each visit to the clinic with attention centered on environmental, food, and psychosomatic factors that might be contributory; but no clue was apparent. A review of the charted attacks, however, brought to attention the fact that many of the severe ones occurred on Fridays, the day he was treated at the clinic. The possibility of aggravation from the dust and vaccine injections was considered, and the doses were reduced materially; but there was no change in symptoms, nor were the symptoms ameliorated by injections of only buffered saline.

Again the foods eaten came into question, and it was found that on Fridays only he was eating American cheese. This he was told to eliminate.

On the following weekly visit to the clinic he reported that for the first

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time in more than two years of treatment he had spent a comfortable week, From then on he continued asymptomatic for eleven weeks, when he was instructed to eat the same kind of cheese. Two hours after the ingestion of the cheese he got an attack of asthma, lasting thirty-six hours, relieved by epinephrine and Tedral. Elimination of this food was again followed by a period of freedom from attacks for eight months. A second deliberate feeding of it provoked a new attack of shorter duration and severity. A third deliberate feeding resulted in similar symptoms, while elimination of this food gave freedom from attacks.

In order to further prove that the cessation of symptoms upon the elimination of the offending food and the recurrence of symptoms on deliberate feeding of it was not predicated upon a psychic factor, it was given to him as grated cheese in colored capsules to conceal the contents. As he had at various times been given different capsules at the clinic, this was only one more occasion and did not arouse any curiosity. Three hours after the ingestion of the capsules, roughly an average portion of cheese, he got an attack of asthma of moderate severity which wore off in two days. Tedral taken every three hours gave him relief. At this writing he has again been symptom free for more than six months.

The outstanding things in this case, noticed shortly after the asthmatic attacks were controlled, were that the patient began to gain weight and increase in height and the pronounced scaliness of the skin began to diminish. He now has gained close to twelve pounds in weight and four to five inches in height. His looks are beginning to approximate his actual age. His mental adjustment parallels his physical gain. His skin is markedly softer, more pliable, and with very few scales.

DISCUSSION

Food sensitivity, unlike pollen and inhalant sensitivity, is difficult to prove even in the presence of a clinical history or positive direct and indirect reactions. Skin positive and clinically negative cases exist, and vice versa. This is a case of clinically proven food sensitivity illustrating that the most dependable test in food-sensitive cases is the clinical one. Cessation of symptoms on elimination of a food and the reproduction of the same allergic manifestations on repeated occasions upon deliberate feeding of the same substance is the only positive proof of the food being the exciting agent.

However, this case is presented primarily to emphasize the importance of searching for the specific allergen. While this patient was treated by eliminating foods found positive on skin testing, as well as some other known food offenders, inhalants, and contactants, and by the accepted medications and oxygen with but little relief, it was the removal of the specific allergen that influenced favorably not only the specific shock organ but also the entire economy as described.

SUMMARY

A case of clinically proven food sensitivity is presented. The influence of this sensitivity not only on the specific shock organ, the bronchi, but on the nutrition, growth, skin condition, and mental attitude of the patient is described.

The necessity for diligent search for the specific causative agent is emphasized.

357 Eastern Parkway

THE AMERICAN RED CROSS AND POLIO

New hope for children exposed to polio is flowing into thousands of Red Cross blood bottles across the nation. The Red Cross has undertaken a dramatic expansion of its blood collections to make available for prevention of paralysis from polio all the gamma globulin that can be obtained from limited present processing facilities.

Recent experiments sponsored by the National Foundation for Infantile Paralysis and using globulin provided by the Red Cross have demonstrated that gamma globulin, produced from the pooled blood of many persons, contains antibodies that attack one or more of the three strains of polio virus so far discovered. A dose of the serum, which requires approximately one pint of blood to produce, protects against the paralyzing effect of polio for about a one- to five-week period.

Last November the Office of Defense Mobilization asked the Red Cross to expand its blood collections to produce as much gamma globulin for all purposes as blood processing laboratories can turn out. Past experience indicates that the disease will reach epidemic proportions in about 150 counties and that some 2,000,000 children may be exposed to it.

The Red Cross will not allocate or distribute the globulin.

Since the amount of globulin needed will far exceed the expected supply, its allocation and distribution will be handled by an agency other than the Red Cross. The agency will be designated by the Office of Defense Mobilization.

The Red Cross *also* must continue to collect blood to meet the needs of civilian hospitals, of the Korean-wounded, and of the nation's plasma reserve. The total program will require approximately 5,000,000 pints of blood and will cost the Red Cross about $18,000,000 next year.

This project is only one of many Red Cross activities and the money only a portion of the much-needed $93,000,000 to carry on the humanitarian efforts of the American Red Cross.

Complete co-operation is necessary to make the blood collections and fund campaign successful. Have YOU made your contribution?

A COMPREHENSIVE SURVEY OF THE INCIDENCE OF FUNGUS SPORES IN THE NEW BRUNSWICK, NEW JERSEY, AREA

SYRIL BRUSKIN, M.A.
New Brunswick, New Jersey

ALLERGISTS and plant pathologists are both vitally in need of more statistics and detailed data concerning the prevalence of airborne flora, its amounts, types, and seasonal variation in this area. Prompted and encouraged by the department of Plant Pathology at Rutgers, and by members of the New Jersey Allergy Association, a preliminary investigation of the air fungus spore population of New Brunswick has been undertaken. At the time of this report, statistics for twenty-one months have been compiled covering two summer seasons completely and one winter season for the years 1950 and 1951.

Petri dish plating of the air sampled was used as a means of identification, thereby limiting the list of genera found to culturable organisms. This excluded obligate parasites of the Basidiomycetes, such as rusts, smuts and mildews, which do not produce fruiting bodies in culture. These may be identified from celluloid strips run in conjunction with the plate technique, but as yet the data are not ready to be included in a report.

METHODS

Collection of spores is made through a Wells Air Centrifuge run at a speed of 1.4 cubic feet per minute. All figures are subsequently reduced to one cubic foot per minute. The machine is exposed on a small platform attached to the windowsill of a third floor laboratory, facing west and overlooking a residential area. Five and ten-minute runs are made on Monday and Friday of each week between 9:00 and 10:00 A.M. The spores are centrifuged into a bottle containing 20 cc of sterile tap water, which is plated out immediately into five petri dishes with Czapek's agar. The bottle is then rinsed and the 10 cc of rinse water plated out into three more dishes. The two runs make a total of sixteen plates, fifteen minutes, and twenty-one cubic feet of air sampled each day. The plates are incubated at room temperature for one week during the summer and two weeks during the winter months, after which counts are recorded and the colonies identified by gross and microscopic examination. Species identification is not often attempted, and the organisms are listed under generic groupings. Unidentifiable or nonsporulating colonies are numbered and subcultured.

Meteorological observations which might affect the spore count for that day such as temperature, relative humidity, wind direction and velocity, and precipitation, and the general climatic picture of the days between runs and

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during the run are recorded at the time of the run. Also included are any reports of major disturbances such as hurricanes which, although not in the immediate vicinity, might affect the spore dispersal.

RESULTS

At present fifty-two genera are represented, mainly organisms classed as Fungi Imperfecti along with a few Ascomycetes and Phycomycetes. Several species of the same genus have been reported, and some genera have been collected only once or twice. Of these fifty-two, twelve genera stand out as the major and most frequently collected organisms. They comprise 92 per cent of the total spore population for the twenty-one month sampling period. Listed in descending order of their frequency, they are as follows:

1. Hormodendrum
2. Penicillium
3. Epicoccum
4. Alternaria
5. Pullularia
6. Aspergillus
7. Stemphylium
8. Botrytis
9. Cylindrocarpon
10. Fusarium
11. Helminthosporium
12. Phoma

Hormodendrum makes up 49.8 per cent of the total spore collection, the other eleven making up 42.2 per cent, and the remaining 7.5 per cent is composed of forty miscellaneous organisms.

The following graphs depict by monthly averages the airborne spore distribution for the twenty-one month sampling period, from May, 1950, through January, 1952. When spore counts are quite low, the 1 cubic foot figures are raised to 10 or 100 cubic feet. The last bar represents the yearly average.

In a number of cases some of the following graphs seem to indicate that counts for the year 1951-52 were higher than those for 1950-51, while others appear to be consistently lower. In an attempt to correlate the weather statistics with these counts, a probable explanation can be arrived at. According to the U. S. Weather Bureau summary, the year 1950 in New Jersey had seven consecutive months below average temperature with the growing season months either much drier or much wetter than normal. The year 1951 was consistently warmer with normal precipitation during the spring months. July, August, and the first part of September were below average in precipitation, but relative humidity was quite high. The first two weeks of December, 1951, and January, 1952, were extremely mild and fairly wet, a situation which is associated with a rise in total spore count due to the appearance of fungus colonies normally collected in the spring or fall.

The theory can also be advanced that fluctuation in spore counts probably are associated with the effect of weather conditions on plants and plant debris during the growing season and their stages of development, upon which plants these airborne spores may be saprophytes or parasites.

A great increase of certain organisms has been reported in plant pathological studies during seasons in which high spore totals have been encountered.

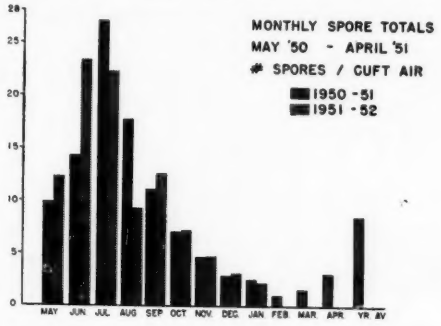

Fig. 1.

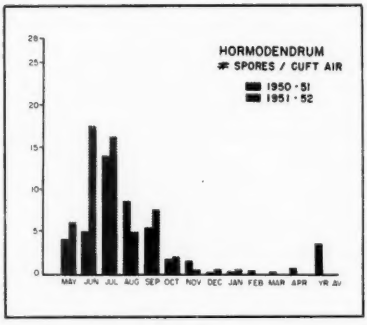

Fig. 2.

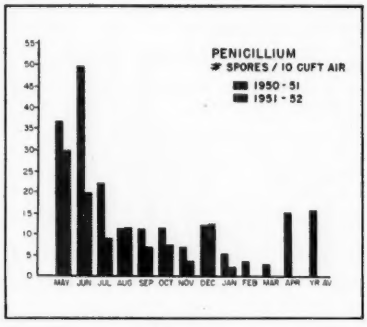

Fig. 3.

MONTHLY SPORE TOTALS

The general spore population seems to follow a fairly set curve (Fig. 1), with some slight variations between the two years. The bulk of the spores were collected between June and September, with a peak occurring in late June and July. The month containing the lowest total was February, which also will be true for subsequent graphs. This general spore population pattern is followed throughout both years with many organisms. The genera which comprise the bulk of each bar on the total count graph, from this preliminary observation, seem to produce spores more readily in a mild and fairly damp environment than in a cold, wet or hot, dry one. Months having temperatures between 40-70° F. and about fourteen to sixteen days of rain, not continuous, seem to be the ones which show the steady rise and peak here.

HORMODENDRUM

The Hormodendrum curve, as is shown here (Fig. 2), closely follows the pattern for the total spore population, also having its peak in June and

July and its low point in December through February. The 1951 counts are in most cases higher than those of 1950, which has been indicated

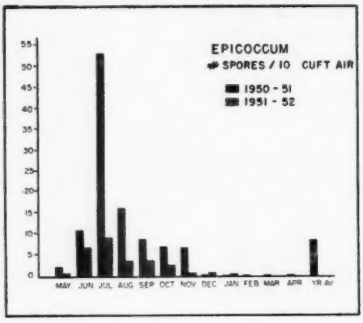

Fig. 4.

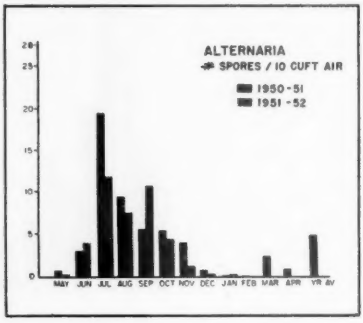

Fig. 5.

before. According to our weather data, higher counts occur in warm weather with moderate dampness. Hot and dry weather invariably seems to produce lower counts, as in August of 1951 as compared with August of 1950, which was cooler and slightly wetter. Unseasonably cold and wet weather seems to lower the count, as in November, 1951. November, 1950, was warmer, with normal precipitation for that month.

PENICILLIUM

Penicillium (Fig. 3), comprising 14.5 per cent of the total population, appears to be present in consistent quantities throughout the year, even in February. During both years the bulk of the spores were collected in April, May and June. The counts for 1951-1952 are lower except for two months, August and December, and the differences here are slight. This seems to indicate that spore production and dissemination of Penicillium and Hormodendrum occur under different optimum conditions.

EPICOCCUM

Epicoccum (Fig. 4) which is 6.9 per cent of the total spore population, makes a sharp rise from May and reaches its peak in July, with a gradual drop to December. The counts during all the winter months remain quite low. Comparison of these figures with the climatological data indicates that this organism is favored by a cool, wet summer, such as the one found in 1950. The slight rise in December, 1951, probably can be attributed to the mild weather which was comparable to favorable spring-like conditions.

ALTERNARIA

The total Alternaria (Fig. 5) spore count for twenty-one months makes up 5.2 per cent of the total spore population. The peak which is reached in July has been reported frequently in aerobiological literature. It is quite

prevalent in the fall and appears occasionally in the winter. The preference probably is for mild, fairly dry weather with humidity about 50 per

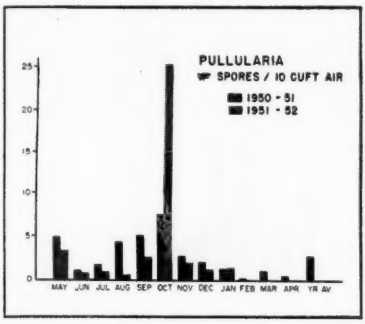

Fig. 6.

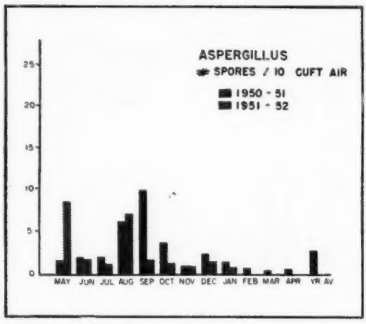

Fig. 7.

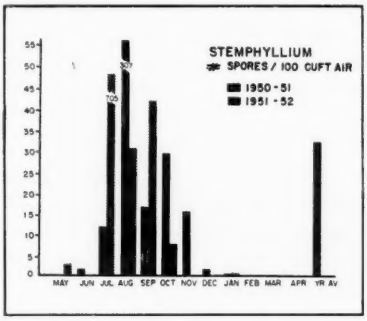

Fig. 8.

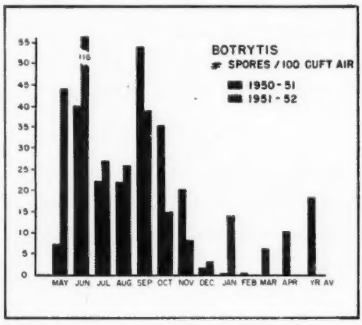

Fig. 9.

cent. Alternaria has been reported in quantity on potatoes in July and August, and New Brunswick is quite close to the New Jersey potato fields.

PULLULARIA

Pullularia (Fig. 6) represents 3.7 per cent of the total spore population for the twenty-one month period. A double peak in the curve appears in May and October, with the fall peak being the higher. Between these two high points there are often "showers" of spores which might raise the count for any individual sampling day. The drop between the two peaks during the hot summer months would seem to indicate that this type of summer weather was detrimental to spore production.

ASPERGILLUS

Aspergillus (Fig. 7) represents 2.8 per cent of the total spore population. It is present in fairly low but consistent numbers all the year. Although the

quantities are lower than those of Penicillium, more species are represented. Maximum spore collection came during August and September, with

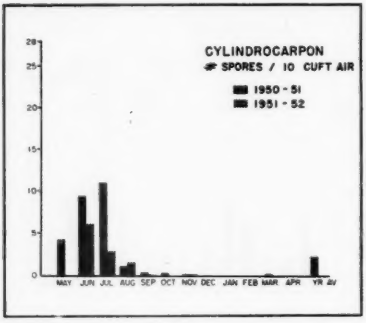

Fig. 10.

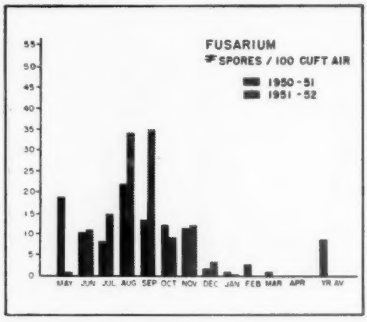

Fig. 11.

a single high point in the unusually warm May of 1951. One would think from this that warm, humid conditions would raise the counts, but such a conclusion cannot be reached here, since the differences in counts under various weather conditions are not sufficiently great.

STEMPHYLIUM

Stemphylium (Fig. 8) comprises 2.7 per cent of the total spore population. The peak is reached in August, with over 90 per cent being collected between July and October. Between February and early May it is completely absent. Stemphylium has been repeatedly reported on tomatoes all during August and September; the rapid decline and finally complete disappearance of airborne spores seems to coincide with seasonal drop in temperature and termination of the growing period.

BOTRYTIS

Botrytis (Fig. 9) makes up 2.6 per cent of the total spores collected. It achieves two peaks, one between May and June and the other between September and October, with the count remaining fairly high over the summer. These spring and fall maxima seem to indicate a preference for mild, humid conditions. During June the organism has been observed on peonies and in the fall on dahlias in residential areas. January of 1952 was exceedingly mild with precipitation greater than normal; these conditions might have been the cause of the rise at that time.

CYLINDROCARPON

Cylindrocarpon (Fig. 10) accounts for 1.8 per cent of the total spore population. The spores of this organism appear mainly during the spring and early summer with a maximum count during late June and early July. It rarely appears after August and not at all during the winter. The

distribution seems to indicate that perhaps it is associated with a plant source.

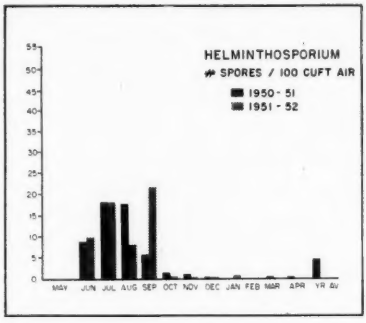

Fig. 12.

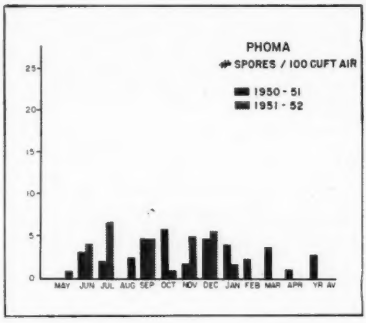

Fig. 13.

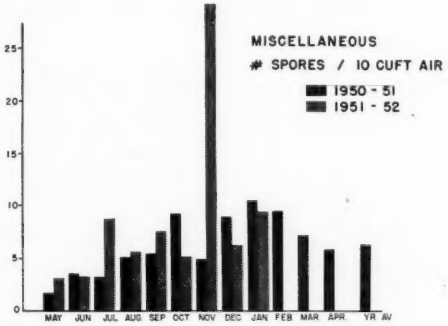

Fig. 14.

FUSARIUM

Fusarium (Fig. 11) makes up only 1.1 per cent of the spore population. The bulk of the spores are collected in the late summer and fall, that is, August through November. This organism is often found on corn, which is growing and in the process of harvesting at this time. December of 1951 was quite mild, and a slight rise in Fusarium colonies was found on the plates.

HELMINTHOSPORIUM

Helminthosporium (Fig. 12) represents only 0.6 per cent of the airborne spore population. The greatest occurrence is in July, August, and September, during which time Helminthosporium has been reported on corn and grains; it is rarely present or is completely absent during the winter. The relative rise in number during September, 1951, as compared to 1950, might be attributed to the warm, fairly wet weather in 1951.

PHOMA

Phoma (Fig. 13) seems quite consistent throughout the year, with a slight increase during the late fall and winter months. This organism is a pycnidial type, the pycnidium probably offering more protection to the spores, enabling them to remain viable during the cold weather. However, Phoma comprises only 0.3 per cent of the spore population.

MISCELLANEOUS SPORES

Forty organisms make up this miscellaneous (Fig. 14) group which represents 7.5 per cent of the total. The peak is shifted to the fall and early winter, in contrast to the counts on the monthly totals graph. This can undoubtedly be explained by the fact that the bulk of the spore population during June, July, and August is composed of Hormodendrum, Penicillium, and Epicoccum. The great rise in November, 1951, was due almost entirely to an unidentified organism which appeared on the plates in great quantities when sampling runs were made during or immediately after a rain.

DISCUSSION OF CLIMATIC EFFECTS ON SPORE COUNTS

It would appear that, unless a major meteorological disturbance occurred, involving a widespread area over several states, most of the variations in spore counts are brought about by the action of local weather such as has been experienced in a city like New Brunswick and surrounding rural areas. Day-to-day changes in the local climate seem to affect plants, plant debris, soil, and dust on buildings and in turn cause changes in the air flora. In large areas such as the great plains where topographical interference is almost nil, it has been reported that a great dispersal of spores by wind occurs. On the other hand, winds traveling over large bodies of water for a considerable time tend to be fairly clean, since the spores fall out and no new ones are picked up. But no conclusive evidence as yet has been derived from this study to indicate that wind direction in itself has an effect on the spore population of the local scene. High wind speed at the point of collection increases the spore count only if preceded by a few days of dry weather, under which conditions the spores are readily carried aloft.

Several hypotheses as to local climatic effects can be set forth as probable explanations for variations in sport counts after examining the results reported herewith. The first of these involves precipitation, its duration, conditions before the rainfall, and the time lapse between its occurrence and the time of sampling. Runs made immediately following a heavy snowfall prove the air to be free of spores, and those taken one or two days after the snow, when a snow cover is still on the ground, are extremely low. If the snow cover persists longer than three or four days, there is a gradual increase in spores again, mostly of Penicillium and Aspergillus.

In nearly all instances of sampling during or immediately following rainfall, it was found that the count drops greatly even in a month where the count is at its peak. When one to three clear, warm days follow a steady one-day rainfall, it is noted that the spore count rises sharply at the end of this time. However, if these warm, dry days persist past five to seven days, the count slowly drops again even though much dust is prevalent. It might be that the dryness is not conducive to spore production in many genera or that airborne spores do not remain viable long under dry conditions. If, however, high relative humidity prevails during this rainless period, the spore count of many of the genera remains moderately high.

Three or more clear days followed by a light rain seem to stimulate spore production, as evidenced by the counts, or, perhaps the rain serves to splash spores from the soil, plants, and buildings into the air. However, if the rain is a heavy one or of long duration, runs taken following it will again be below average. The spores probably are washed out of the air, or stick to the ground.

Lastly, it has been noted that several clear, warm, dry days following several clear, cool ones often result in lower spore counts. It might be that many spore types do not produce spores as readily when exposed to prolonged cool temperatures.

In summing up this survey it can be said that all weather-condition trends given as reasons for influencing the total spore population are derived solely from data accumulated during the twenty-one month period of sampling. It appears from this evidence that spore production of the various organisms follows climatological and seasonal patterns. However, controlled environmental-condition experiments and several more years of sampling would be needed to conclusively confirm these results.

CHANGES IN THE ELECTROCARDIOGRAM SEEN DURING ATTACKS OF MIGRAINE AND THEIR NORMALIZATION BY ERGOTAMINE TARTRATE ADMINISTRATION

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Madrid, Spain

THE PATHOGENESIS of migraine is far from being completely known. Wolff's theory is generally accepted; however, all the phenomena seen during attacks of migraine cannot possibly be explained by this theory. What we know now about the symptomatology is very little, and the mechanism through which ergotamine tartrate (Gynergen) causes cessation of the paroxysms is not fully clarified. It is obvious that migraine as a vegetative symptom complex calls for wider research work.

Any contribution conducive to the elucidation of the pathogensis of these attacks should be given full consideration. The writer has been interested in this subject for many years and has paid special attention to the various clinical aspects of the disease and, lately, to the circulatory disturbances which may accompany this process. One particular patient (Case 1) has been under observation for over twenty years. In 1932 he had prolonged attacks of migraine associated with paroxysms of auricular fibrillation. To my knowledge this observation had not been recorded in medical literature, though Professor Jiménez Díaz[6] quoted my personal communication to him in some of his papers. The patient mentioned above has had long periods of remission but continues to suffer from frequent attacks of migraine which are, however, no longer accompanied by auricular fibrillation. The idea of investigating the possible presence of other changes in the electrocardiogram was stimulated by the special symptomatology of this patient.

The investigation was so conducted that the appearance of alterations in the electrocardiogram and their subsequent evolution could easily be followed after administration of ergotamine. The procedure employed by Nordenfelt[9] was adhered to more or less strictly.

As is known, this test is carried out by injecting 0.5 cc (0.25 mg) of ergotamine intramuscularly with the patient in the recumbent position. The basal electrocardiogram is taken prior to the injection and is repeated fifteen and thirty minutes later. Three different results may be obtained, as follows: (1) Complete normalization of previously altered T-waves; an organic lesion of the myocardium is then highly improbable. (2) Partial normalization; a functional component or organic lesion should then be suspected. (3) The abnormal electrocardiogram persists, or a previously normal tracing is altered; this should be regarded as evidence of the presence of an organic lesion. The significance of the test concerning the

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organic or functional nature of the disturbance recorded in the electrocardiogram and the interpretation of the mechanism will be discussed hereafter.

The interpretation of the results in our cases is no problem, since the changes we recorded are, as reported below, totally and quickly reversible. It is beyond doubt, therefore, that these changes belong to the functional group. A more extensive knowledge of the mechanism of action of ergotamine on the electrocardiogram would be of great assistance, but we shall return to this point later.

METHODS

Electrocardiographic examinations were made of five patients suffering from migraine. Tracings were recorded before and during the attack. One electrocardiogram was taken in the middle of the attack before any drug was administered; subsequent tracings were made at various intervals after the intramuscular injection of 0.5 cc (0.25 mg) of ergotamine tartrate. Several tests were carried out on Case 1, the patient who exhibited paroxysms of auricular fibrillation during his attacks of migraine.

The clinical history is also given of a patient on whom an electrocardiographic examination could not be carried out at the time. Her anamnesis, however, permits the assumption that she has paroxysms of auricular fibrillation during her migraine attacks.

CASE REPORTS

Case 1.—A man, aged forty-eight years, has been suffering from migraine since the age of seven. In his childhood the attacks were accompanied by vomiting. Later vomiting was rare. He had prolonged and severe attacks of infrequent character until he was twenty-two; since then the attacks have become more and more frequent. At the age of twenty-eight (in 1932) he went through a period of extremely frequent attacks (two to three weekly). These attacks lasted for over twelve hours before he became aware of the presence of "arrhythmias" which either disappeared when the attack was over or else subsided the following day. The electrocardiogram shown in Figure 1-A was taken during such an episode of paroxysmal auricular fibrillation. On the following day, a new electrocardiogram was taken (Fig. 1-B). In spite of the fact that the rhythm was now normal the tracings show some vestiges of the previous disturbances: T_1 diaphasic; T_2 and T_3, isoelectric. Complete normalization took place several days later (Fig. 1-C).

A general clinical follow-up study was made in 1950. The electrocardiogram shown in Figure 2 was taken for control purposes when the patient had no attacks. Four series of electrocardiograms were then taken during attacks according to the procedure mentioned above. In order to save space a description is given only of test No. 3. In this test the orthostatic effects and the action of Hydergine were studied as well.

Test No. 3 was carried out on February 2, 1952, eight hours after the attack of migraine had commenced. The first electrocardiogram was recorded with the patient lying down, the second with the patient standing up, and the third after the patient had been in the upright stance for five minutes. Immediately following the taking of these tracings, 1 cc of Hydergine was injected intramuscularly. The fourth electrocardiogram was recorded with the patient lying down thirty minutes after the injection. An intramuscular injection of 0.5 cc of ergotamine tartrate was then given

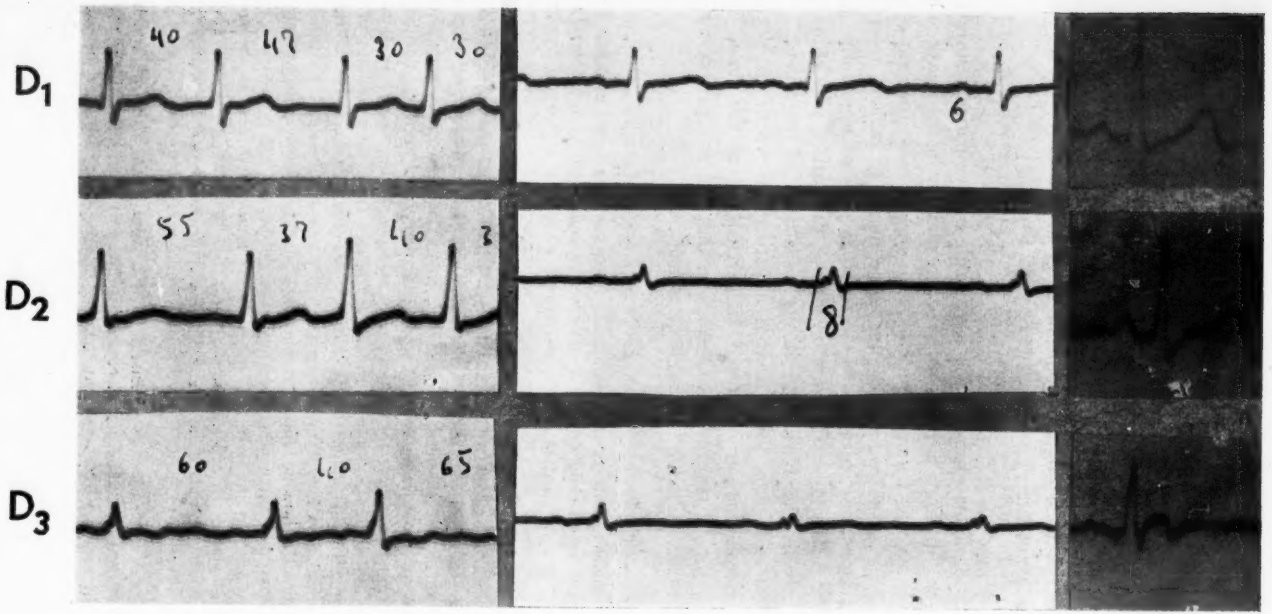

Fig. 1. Case 1. Paroxysmal auricular fibrillation during headache and electrocardiographic evolution towards normality (1932).

and the fifth electrocardiogram taken fifteen minutes afterwards. The sixth electrocardiogram followed five minutes later with the patient standing up. The seventh electrocardiogram was recorded thirty minutes after the ergotamine administration with the patient lying down (Fig. 3). Other electrocardiograms obtained during a

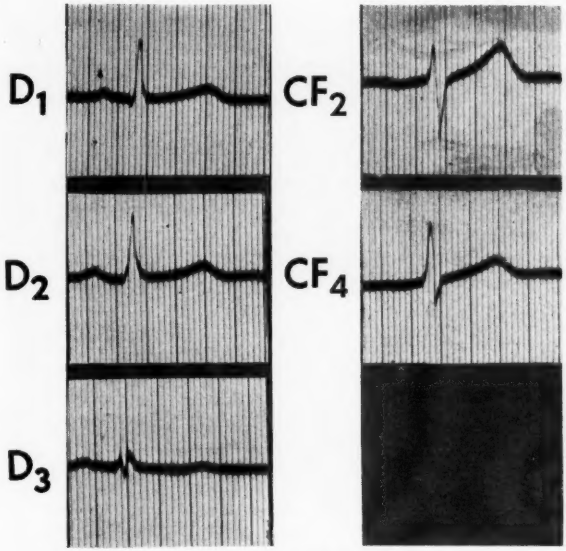

Fig. 2. Normal electrocardiogram of Case 1 (1952).

moderate attack were normal. In a fourth episode the alterations were distinctive, though the tracings which had been obtained some hours earlier were normal.

Case 2.—A man, aged thirty-six, had attacks which started in puberty and never occurred more than once a week. Very occasionally he had to stay in bed on account of the pain, which disappeared quickly on administration of Gynergen. Of late, however, more than an hour passed before the attacks subsided. The attacks were not accompanied either by vomiting or circulatory disturbances.

A control electrocardiogram was taken when the patient was normal on February 18, 1952. A test was carried out seven hours after the attack of migraine had started on February 24, 1952: the first electrocardiogram was taken while the patient was at rest, the second fifteen minutes after injecting Gynergen, the third thirty minutes after the injection, and the fourth sixty minutes after injection.

Case 3.—A man, aged fifty-two years, gave a history of frequent attacks in his youth, becoming less frequent later. Three years ago they became more frequent again, and were of moderate severity. They were not accompanied by vomiting, and Gynergen was effective. The control electrocardiograms did not differ from those taken during the course of the test, and all were normal. The attacks were accompanied by hypertensive crises which persisted twelve to fourteen hours after the attack had subsided as a result of ergotamine administration. In one of the episodes an intramuscular injection of 1 cc (0.3 mg) of Hydergine was given in order to ascer-

Fig. 3. Case 1, third test (1952), (A) during attack with patient lying down; (B) with patient standing up; (C) thirty minutes after intramuscular injection of Hydergine; (D) fifteen minutes after intramuscular injection of Hydergine.

tain its effects. Cephalalgia did not abate, but the following changes occurred in blood pressure: when first measured it was 175/115 mm Hg; five minutes after the injection, 150/100; and fifteen minutes later, 130/90. Subsequent injection of ergotamine did not modify blood pressure, but the headache disappeared.

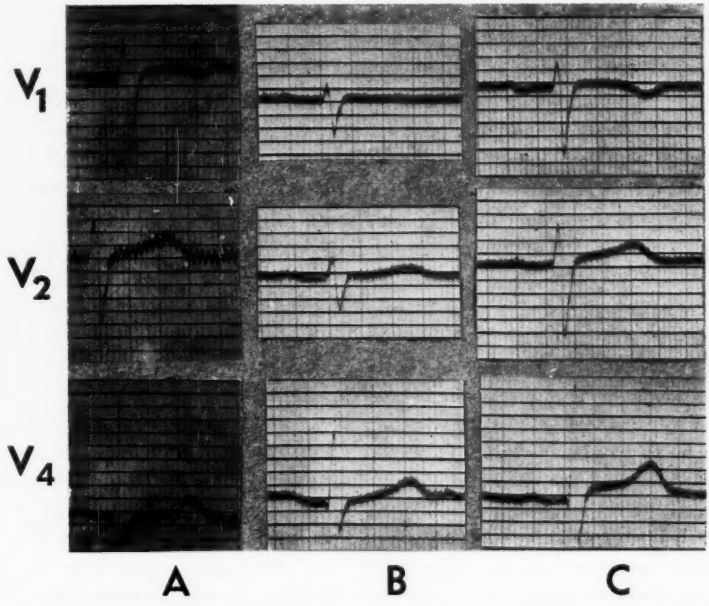

Fig. 4. Case 6 (1952). (A) unipolar precordial leads when normal; (B) the same leads during attack; (C) fifteen minutes after intramuscular injection of Hydergine.

Case 4.—A twenty-five-year-old woman had premenstrual attacks of migraine sometimes accompanied by vertigo. The control electrocardiograms did not differ from those obtained during the attacks.

Case 5.—A woman, aged thirty-two, had prolonged and severe attacks of migraine which never appeared more than once a month. *She had never received ergotamine injections.* Her history revealed that she had "arrhythmias" at the end of the attacks. In one of these attacks an electrocardiogram was taken by a Seville cardiologist (Dr. Vela) who prescribed Quinicardine. We did not have the opportunity of examining the patient from an electrocardiographic point of view, but there was sufficient evidence to assume that she suffered from auricular fibrillation in the course of her migraine attacks.

Case 6.—A sixty-year-old woman had severe attacks twice a week. Gynergen was effective in combating these attacks. A normal electrocardiogram was obtained before the attacks and the electrocardiogram taken during the attacks shows the characteristic changes in V_1, V_2 and V_4. No such changes appear in the electrocardiograms taken fifteen, thirty and sixty minutes afterward (Fig. 4).

DISCUSSION

Some comments will be made below concerning the period in which the paroxysms of auricular fibrillation occurred. Apart from this, the electrocardiographic changes recorded in the course of attacks of migraine are characteristic in Cases 1 and 6, and also in Case 2, though less marked. No changes occur in Cases 3 and 4, nor do changes appear in the electrocardiogram obtained during a moderate attack of migraine in Case 1.

As may be gathered from the electrocardiographic specimens reproduced in this paper, the alterations consist essentially of a slight decrease in the total potential. This phenomenon appeared only if the precordial leads were used and quickly became normal after the injection of ergotamine.

Figure 3 shows that the only deflections seen when using leads CF_2 and CF_4 are restricted to a minimum QRS complex, especially in CF_2. Neither P- nor T-waves were present.

In addition to this, in the fourth test it could be demonstrated that the changes are similar in the CF_2 and V_2 leads as well as in CF_4 and V_4. The most striking observation is the rapid normalization of the tracings following the administration of ergotamine.

The third test was of great assistance in ascertaining orthostatic alterations. It may be seen that T_1 and T_2 waves disappeared (some complexes include a negative T_1 wave with a downward ST_1 segment) and that R_1 and R_2 waves are greatly diminished. Orthostasis had no effect whatsoever on the electrocardiograms taken from precordial leads. The effect of the intramuscular injection of Hydergine was also tested in this experiment. A slight deflection corresponding to the T-wave appeared, but the headache did not disappear. On the contrary, fifteen minutes after ergotamine had been injected the tracings recorded from any lead were normal though the headache had not yet abated. The electrocardiogram taken in orthostasis was also normal, and the change in position did not modify the tracing.

In Case 2, the only difference between the control electrocardiogram and those obtained in the course of the attack consists of a diminution in the entire ventricular complex. This complex increased remarkably after the injection of ergotamine, as seen in CF_2, though the headache still persisted at the time.

In Cases 3 and 4 no modifications of the electrocardiograms taken during the attacks of migraine were seen; however, the fact has to be taken into account that these attacks were not as severe as those of Case 1. In Case 3, Hydergine completely combated the hypertensive crisis. In other crises, however, the blood pressure was not modified either spontaneously or when the headache had disappeared after ergotamine administration.

The modifications described in the unipolar precordial leads of Case 1 are seen with similar intensity in Case 6.

Because these phenomena are rare, it is worthwhile emphasizing that every precaution was taken in the course of the tests to eliminate all

possible technical errors such as could occur at the points on the chest where the leads are taken, preparation of the skin, et cetera. There is little room for doubt since each test consists of a series of tracings in which the technical steps involved in the procedure were repeated exactly. It is also significant that, regarding Case 1, the number of tests carried out was sufficient to confirm the presence of the phenomenon in different degrees of intensity, whereas in other patients normal tracings were obtained with the same technique. In our opinion it is beyond doubt that such phenomena exist though their meaning is difficult to interpret.

In the medical literature we were able to consult, no similar phenomenon is recorded. We were unable to find any paper describing electrocardiograms taken *during* an attack of migraine. Obviously many electrocardiograms have been taken of patients suffering from migraine, but no reference is made to positive findings obtained during the attacks. The relative infrequency of the phenomenon and the time necessary to run a successful test have to be taken into account. The changes in the T-wave reported by Frischknecht[3] in cases of whooping cough which became normal on administration of Hydergine, were seen in six cases only of twenty children whose electrocardiograms were taken.

COMMENTS

It is difficult to interpret the above-mentioned phenomenon.

After a series of contradictory results concerning the influence of the autonomic nervous system on the electrocardiogram, most authors agree that sympatheticotonia gives rise, apart from other changes, to a low isoelectric or even downward T-wave and that this phenomenon can be corrected by the administration of sympathicolytic drugs, especially by the alkaloids obtained from ergot of rye.

Therefore, if the electrocardiographic alterations recorded in cases of migraine consisted only of a depression of the ST segment and a small potential or even downward deflection of the T-wave, they might be considered sympathicotonic electrocardiograms, since all such alterations are normalized when ergotamine is given. These cases of sympatheticotonia might be compared with the vegetative changes without paroxysms and those described by Frischknecht in cases of whooping cough[3] or of poliomyelitis.[4] This is true of the alterations found in the second part of the ventricular complex, in the repolarization phase. But it is most remarkable when using the precordial leads that the QRS complex is of very low potential and quickly becomes normal after the injection of ergotamine. Such normalization parallels that of the T-wave.

All the papers dealing with the action of the autonomic nervous system on the electrocardiogram are exclusively concerned with the final phase of the ventricular complex. Moreover, Zeh[17] and Ströder[16] point out that the changes in the QRS complex have no relation whatsoever to changes

in the autonomic nervous system. These authors occasionally refer to deflections greater than normal, but they do not describe low potential tracings. In the alterations we have observed, low potential plays a predominant role. The conclusion to be drawn, therefore, is that these alterations are similar and, according to the ideas accepted at present, are due to adrenosympatheticotonic action.

Harkavy and Romanoff[5] include the QRS complex changes in the reversible electrocardiographic pattern that appear in bronchial asthma. Among these changes is low potential. This is not, however, evident in the illustrations included in this paper.

Nevertheless, in the tracings obtained during the attacks by means of precordial leads, such change is fundamental and should, therefore, be listed among the reversible paroxysmal vegetative changes. Its interpretation would imply a revision of the mechanism of low potential (L.P.) production. It may be worthwhile to point out that at present the alleged increase in electric resistance between the heart muscle and the lead in cases of myxedema and pericarditis with effusion is not regarded as significant. This can be accounted for by the fact that in myxedema the same potentials are obtained when needles are used as leads, thus overcoming the resistance furnished by the skin. In regard to pericarditis with effusion, one should bear in mind that the heart muscle is not electrically isolated on account of the effusion since this effusion does not consist of distilled water but of a denser fluid. This fluid, because of its electrolyte content, is an excellent conductor and comparable to the saline water bath in which the limbs are submerged.

The low potential can be explained by the compression of the blood vessels of the myocardium and the fact that the restricted diastolic dilation of the heart is an obstacle to normal function, since normal diastolic dilation is essential to the coronary blood flow.

Apart from these cases and others in which low potential is due to toxic effects on the myocardium (diphtheria, rheumatic fever, cancerous cachexia) because of interference with normal oxygen supply, low potential is almost exclusively due to coronary arteriosclerosis, as was demonstrated in the work of L. G. Steuer,[15] which included fifty cases of low potential electrocardiograms. A histopathological study of these cases was carried out.

It is therefore possible that in our experiments an ischemia of the myocardium is responsible for the phenomenon and that the electrocardiogram taken during the attack corresponds to a hypoxemia tracing which, as is known, may become normal after the administration of ergot alkaloids.

Regarding asthma, Harkavy and Romanoff[5] give importance to a possible allergic reaction in the coronary blood vessels capable of giving rise to insufficiency due to spasm or edema.

Whatever the mechanism of production we are unable to find out the reason for the fact that the phenomenon occurs in precordial leads only.

It is beyond doubt that the headache paroxysm involves the entire body. We should like only to point out the changes in the carbohydrate metabolism and acetonuria as seen by us in 1930[6] as well as the changes in the secretion of urine, and the significant alterations of the capillaries observed by Redisch and Pelzer.[11] With reference to the latter, Professor Kennedy says that the phenomenon is so characteristic that the side of the head affected by migraine may be diagnosed by digital capillaroscopy.

The electrocardiographic changes described are yet another phenomenon in this clinical entity. They may be regarded as adrenosympatheticotonic, which would call for further research concerning a possible relationship between these changes and the elimination during the attacks of substances whose action is similar to acetylcholine (demonstrated by Jiménez Díaz, et al.[7]).

On the other hand we now know, thanks to the investigations of Raab,[10] that adrenaline gives rise to intracellular edema of the myocardium, thus facilitating the occurrence of anoxia, and to a decrease in the creatine and phosphagen levels, et cetera. These changes must no doubt be reflected in the electrocardiogram. The fact that crises must be prolonged over several hours for the electrocardiogram to show distinctive alterations (and the paroxysmal arterial hypertension which was also present in three cases) leads to the assumption that the above mechanism may also be involved. The quick reversion of the phenomenon is, however, against such a view.

The work of Schimert[13] and of Schimert and Zickgraf[14] shows that adrenaline diminishes what Schimert calls "coronary reserve" since the O_2 requirements of the myocardium are increased 100 per cent, whereas the coronary blood supply is increased 40 per cent only.

If the mechanism through which ergotamine causes the reversion of the electrocardiographic disturbances were known, the problem would be easier to solve. Ergotamine is a substance of complex action. Among the numerous pharmacologic papers on this alkaloid, those of de Vleeschhouwer,[1] Donatelli[2] and Rothlin and Cerletti,[12] deserve special attention. These authors agree that the drug blocks adrenergic action by inhibiting and even reversing the adrenosympathetic effects. Rothlin contends that a central nervous system action is responsible for the changes on the electrocardiogram. Such action would be due to activation of the center of the vagus, since in the heart and lung preparations the adrenaline action cannot be blocked with ergotamine even when the doses are one hundred times as high as those necessary to inhibit the vasoconstrictor action on the carotid.

The electrocardiographic changes brought about by ergotamine cannot, therefore, be ascribed to a *peripheral* interruption of the neurohumoral sympathetic impulses. This applies to the electrocardiogram taken while the patient is lying down and at rest. Regarding the orthostatic alterations

and the effort and hypoxemia electrocardiograms, one should in addition take into account the inhibitory action of ergotamine on the proprioceptive heart reflexes.

This alkaloid has, therefore, an action on the central nervous system (stimulation of vagal centers or inhibition of sympathetic centers), inhibition of the circulatory pressoreceptor reflex centers, and peripheral adrenosympathicolytic action on the vessels. This complex action of ergotamine is of no assistance in solving the problem of how the electrocardiographic changes we observed were produced. We feel inclined, however, to think of an "adrenotoxic" effect.

Auricular fibrillation is a different problem, and we may point out (1) auricular fibrillation occurred only during extremely prolonged attacks of migraine, and (2) its occurrence is not related to administration of ergotamine.

In Case 1, the patient had several attacks of auricular fibrillation several years ago, but no longer had them since he started taking ergotamine in the treatment of his headaches. In Case 5, the patient never received ergotamine, but it may be assumed that she had attacks of auricular fibrillation. This does not necessarily imply that once the mechanism responsible for auricular fibrillation is in progress, the condition must follow the administration of ergotamine; however, the electrocardiograms and clinical data of Case 1 indicate that the cardiac disturbances responsible for the abnormal tracings may, if not interfered with, give rise to auricular fibrillation some hours afterwards. Manning and Caudwell[8] induced auricular fibrillation by ligation of the circumflex branch of the left-side coronary artery of the dog, or by electric stimulation with 50 volts for five minutes in the guinea pig, and were able to inhibit fibrillation by pretreatment with ergotamine or DHE 45. We have seen that headache by itself is capable of inducing auricular fibrillation and that ergotamine may prevent occurrence of this condition.

SUMMARY

1. A description is given of electrocardiographic changes seen during prolonged and severe attacks of migraine. The patients did not exhibit any organic lesion in the circulatory system, and their electrocardiograms were normal before and after the attacks.

2. The changes consist of low T-wave potential and marked decrease of the total potential in the precordial leads. It is emphasized that this phenomenon is rare not only in regard to paroxysmal occurrence of low potential but also in regard to its presence in precordial leads only. These phenomena are not accompanied by subjective sensations on the part of the circulatory system.

3. Electrocardiographic changes, as well as the migraine headache, are quickly reversible after the intramuscular injection of 0.5 cc (0.25 mg) of

ergotamine tartrate, a drug which has both vasoconstrictor and sympathicolytic actions. The electrocardiographic changes as well as the migraine attacks are not reversible (or only very slightly reversible) after the injection of 1 cc (0.3 mg) of Hydergine, which has vasodilator and sympathicolytic properties.

4. The hypothesis is made that electrocardiographic changes may be related to the development of an adrenosympatheticotonic condition during the headache.

5. Paroxysmal episodes of auricular fibrillation have been observed during attacks of migraine in a patient kept under observation for over twenty years. These episodes occurred before ergotamine was used. They no longer appeared after the patient used this drug to abolish the attacks.

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NEW SLOW ACTING EPINEPHRINE SOLUTIONS

Results of Therapy with Modified Epinephrine Preparations

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IN a previous publication[3] experimental studies were reported which demonstrated that the action of therapeutic agents could be modified by combining them with solutions of algin. Algin is the common name for derivatives of alginic acid, such as the sodium, potassium and ammonium salts, as well as the propylene glycol ester. (The propylene glycol ester has been extensively used in the studies to be reported. Previous studies with propylene glycol esters have shown them to be nontoxic.)[1] Alginic acid is the hydrophilic colloidal polymer of anhydro-β-D-manuronic acid and is extracted from brown algae, particularly the giant kelp, *Macrocystis pyrifera*. Algin solutions have many unusual properties, and the addition of small amounts of algin to aqueous solutions increases their viscosity. They are used extensively as thickening, suspending, stabilizing, emulsifying, gel-producing, film-forming, and adhesive agents in numerous commercial and industrial products. Algin is present in many foods, such as ice creams, sherberts, ices, chocolate milk, cheeses, puddings, bakery goods, confectioneries, jellies, syrups, flavor emulsions, salad dressings, meat sauces, meringues, and toppings, and can be found in such products as shampoos, shaving creams, and toothpastes.

Algin solutions maintain their smooth-flow characteristics over wide temperature ranges and do not coagulate or gel on heating or cooling. They are soluble in hot or cold water and therefore allow for ease of parenteral administration with syringe and needle. They are clear, colorless, and free of nitrogen, and have low allergenicity.[2]

METHOD OF STUDY

A variety of medications in combination with sterile saline algin solutions have been compounded, such as medications for allergic disorders: epinephrine, ephedrine, antihistamines, aminophylline, histamine, and allergenic extracts; also antibiotics, hormones, anticoagulants, analgesics, local anesthetics, vitamins, and miscellaneous medications. Mixtures have been prepared for parenteral, oral, rectal, and topical use. It has also been possible to prepare mixtures of aqueous solutions and oily suspensions and maintain them in an emulsified or colloidal state. However, this paper

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will be confined to reporting the results of experiments with algin solutions of varying concentrations and epinephrine of varying strength, hereafter called "Algin-ephrin" for purposes of brevity. Algin solutions vary-

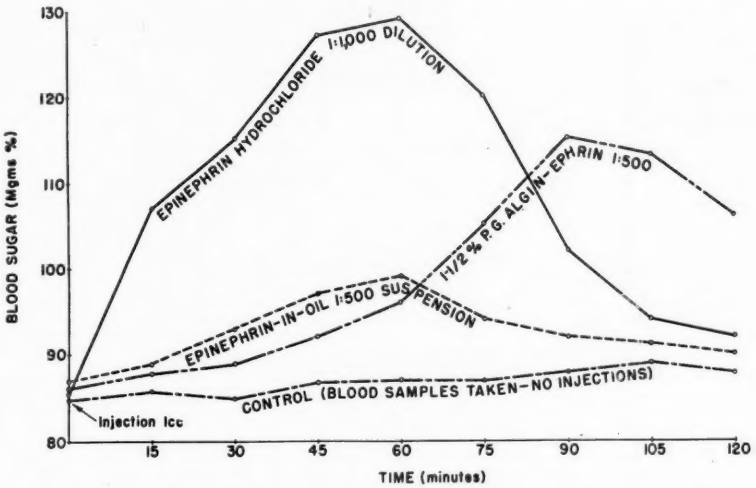

Fig. 1. Comparison of Algin-ephrin, epinephrine HCl, and epinephrine-in-oil.

ing in concentrations from 1/2 per cent to 2 per cent and epinephrine in strength varying from 1:200 to 1:1,000 have been used in these studies. An example of the type of Algin-ephrin solution used follows:

Propylene glycol alginate	1½ %
Epinephrine hydrochloride	1:500
Sodium chloride	0.89 %
Phenol	0.4 %
Sodium bisulfite	0.1 %
Chlorobutanol	0.1 %

The solutions were prepared sterilely and made physiological by the addition of appropriate amounts of sodium chloride. Phenol and chlorobutanol were added for bacteriostasis and sodium bisulfite for color stabilization.

Numerous animal experiments were carried out, and the action of these solutions was compared to that of epinephrine hydrochloride (1:1000) and a conventional suspension of epinephrine in oil. The effects following the intramuscular injection of comparable amounts of the solutions were noted. The reactions on the blood sugar levels and other physiologic responses were recorded.

Patients with asthma, urticaria, and other allergic disorders also received injections of Algin-ephrin solutions. An attempt was made to control these experiments by comparing the effect of plain epinephrine and Algin-ephrin in comparable situations.

RESULTS OF STUDY

The response of the blood sugar of rabbits injected intramuscularly with epinephrine hydrochloride 1:1000, a suspension of epinephrine-in-oil, and

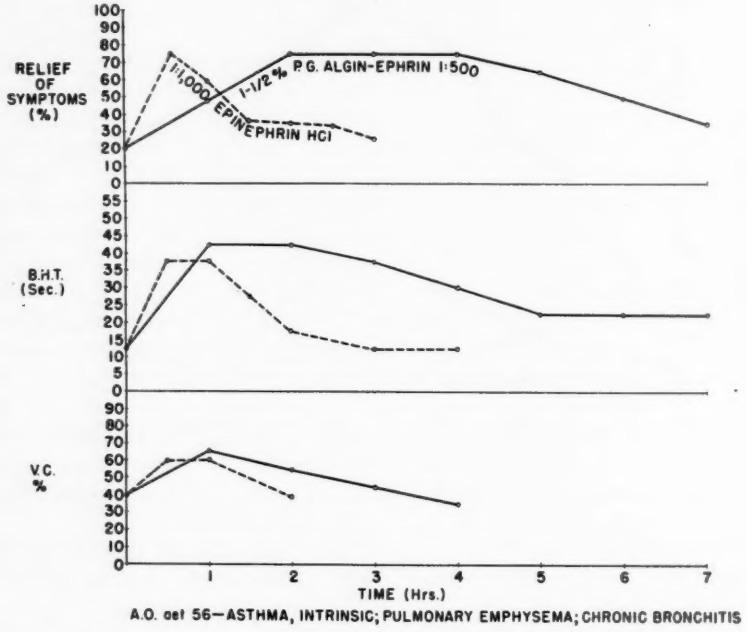

Fig. 2. Comparison of Algin-ephrin and epinephrine HCl in asthma.

Algin-ephrin in comparable amounts is illustrated in Fig. 1. It is noted that an immediate and prompt rise and fairly rapid fall occurs after injection of epinephrine hydrochloride, 1:1000 dilution. The rise with a suspension of 1:500 epinephrine-in-oil is not particularly marked and not greatly sustained. Following the injection of a solution of Algin-ephrin with an epinephrine strength of 1:500 and a concentration of 1½ per cent propylene glycol alginate, there is a substantial, well-sustained rise in the blood sugar. (Pulse rate and nervous reaction in the animals coincided with the levels of blood sugar.)

Fig. 2 illustrates the effect of the injection of a 1½ per cent propylene glycol alginate solution with an epinephrine strength of 1:500 upon a patient with asthma, emphysema, and chronic bronchitis in comparison with epinephrine hydrochloride 1:1000, each injection 1/2 cc, in comparable attacks of asthma. It will be noted that the effect upon the breath-holding time and vital capacity, as well as the degree of comfort of the patient, was markedly prolonged by the use of Algin-ephrin.

The use of Algin-ephrin in urticaria is shown in Fig 3. The patient received "plain" epinephrine and within two hours required another injection because of a return of symptoms. The second injection was a

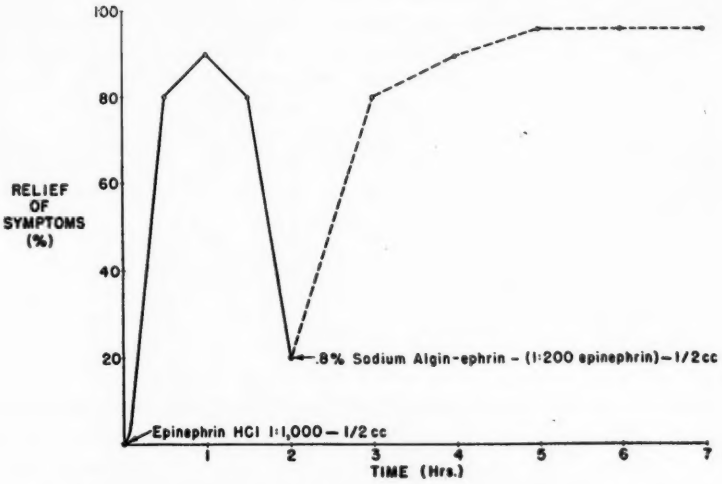

Fig. 3. Comparison of Algin-ephrin and epinephrine in urticarial attack.

comparable amount of Algin-ephrin (with an epinephrine strength of 1:200 and 0.8 per cent sodium alginate concentration). Prolongation of action was evidenced by the fact that no further injections in the subsequent twenty-four hours were necessary. (It is not to be concluded that the epinephrine effect from an injection of Algin-ephrin may last as long as twenty-four hours, however.) This example is included to illustrate that sodium alginate, as well as propylene glycol alginate, is effective and that epinephrine attenuation allowed for the use of a 1:200 dilution.

A composite of three patients, all of whom had chronic asthma, who were habitual users of the conventional forms of "plain" epinephrine and so-called "slow acting" epinephrine suspensions, is shown on Fig. 4. The average length of time of relief obtained from the conventional products as compared to that from Algin-ephrin is recorded. Although there is a considerable variation of response to epinephrine, which commonly occurs, it is noted that the Algin-ephrin response, with the exception of some overlapping, is on the whole more prolonged and slightly more effective than the conventional products in a series of comparable instances.

Patients have received Algin-ephrin with epinephrine strengths varying from 1:200 to 1:1000 with good results. However, it must be emphasized that as the epinephrine strength becomes greater it is advisable to increase

the algin concentration to prevent too rapid absorption. Very slow absorption occurs when the algin concentration of the solution exceeds 1½ per cent.

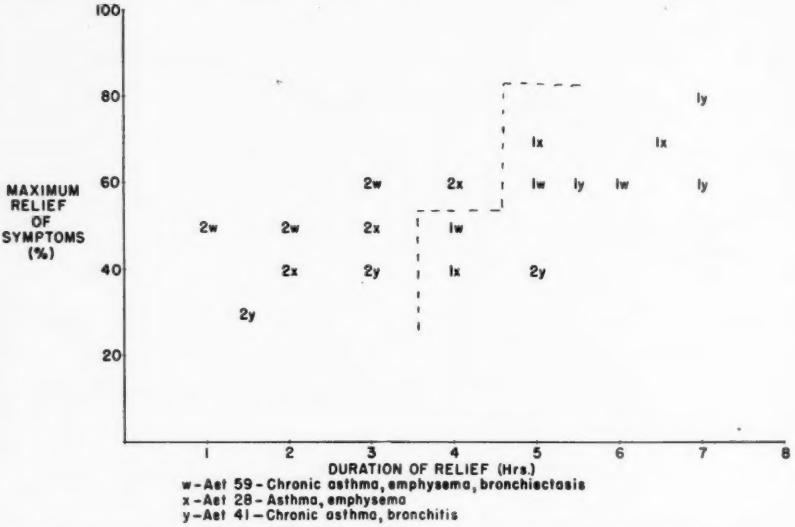

Fig. 4. Comparison of Algin-ephrin and conventional products in chronic asthma.
1 = Algin-ephrin
2 = conventional epinephrine products

CONCLUSIONS

The results of the clinical studies indicate that the new modified solutions of epinephrine in varying strengths combined with algin of various concentrations have a wide range of physiological activity. The greater the concentration of algin the slower the absorption and assimilation, and the more prolonged the therapeutic response. It has been possible to administer larger doses of epinephrine than are conventionally used, thus affording a greater measure of relief to the patient. These solutions are adaptable to situations in which a prolongation of epinephrine effect is desired but can also be prepared to be effective promptly.

DISCUSSION

The new solutions are unique in that two components in the mixture are variable, thus making it possible to obtain a wide range of action. These mixtures have numerous advantages over the conventional so-called "slow acting" preparations. They are water-soluble and can be made physiological by the addition of sodium chloride. They are nontoxic and easily absorbed, nonirritating, painless to administer, and injectable without

preparatory manipulation. Sterilization is easily obtained and sterility maintained. They are free of undesirable foreign matter and are stable within a wide temperature range. They are nitrogen-free, and there is little likelihood of allergic reaction. Also the patient is not likely to have been previously sensitized by the oral or parenteral route, as occurs not infrequently with oil preparations in which epinephrine may be suspended. (Shaking, warming, or other procedures necessary for drugs suspended in a gel or oily vehicle are eliminated.) Uniformity of response is obtained with a minimum of preliminary preparation; and the solutions, although they may be as viscous as oil, maintain free-flowing qualities over wide temperature ranges, making for ease of administration.

SUMMARY

Solutions of algin and epinephrine have been prepared and their physiological and therapeutic actions studied. It has been possible to control the viscosity, as well as the absorption, assimilation, and action of "Alginephrin" mixtures by varying the concentration of algin. Only slight changes in the concentration of algin are necessary to obtain a wide range of physiological activity. Prolongation of therapeutic response has been demonstrated.

The advantages over the conventional preparations of epinephrine are discussed.

The new solutions are adaptable to a wide range of disorders and can be used effectively where immediate, as well as prolonged, action of epinephrine is desired. Larger doses of epinephrine than conventionally used can be given, resulting in more effective relief of symptoms. It is possible to vary the strength of epinephrine as well as to vary the concentration of algin in the mixture. The advantages of having two variables for control of therapeutic response are obvious.

These solutions are effective as therapeutic aids in allergic disorders but are not designed or intended to take the place of the established methods of management of allergic individuals.

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PRANTAL METHYLSULFATE, A NEW PARASYMPATHETIC BLOCKING AGENT, IN THE TREATMENT OF BRONCHIAL ASTHMA

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LITERATURE indicates that the surgical removal of portions of the nerve supply to the lungs has been successful in the management of certain cases of intractable asthma.[2,4,5,7,8,10,11,13] Several surgical procedures have been described, but there is anatomical and experimental evidence that resection of the vagus fibers to the lungs is the procedure of choice.[13]

Attempting to achieve vagal blockade by means of drugs, Blomberg and Lindqvist reported that tetraethylammonium bromide administered intravenously brought about marked improvement in four out of five patients with bronchial asthma.[3] However, repeated intravenous therapy is impractical and there was an apparent need for an orally effective vagal blocking agent.

In 1951, a new anticholinergic drug, Prantal Methylsulfate* (N,N-dimethyl-4-piperidylidene-1,1-diphenylmethane methylsulfate) was announced.[14] This drug was reported to have selectivity of action with a primary effect of inhibiting gastric motility and secretion.[6] Employed clinically for the treatment of peptic ulcer, Prantal Methylsulfate was found to be superior to currently available compounds of similar pharmacologic action by virtue of its relative freedom from side actions.[15] It was our thought that this drug might block the bronchoconstrictor fibers of the vagus and thus provide a "medical vagotomy" which might help certain patients with bronchial asthma.

PROCEDURE OF INVESTIGATION

Seventy-six patients were selected from the authors' two private practices, one of which is devoted to pediatric allergy and the other to adult allergy. At the time of this report, the majority of these patients have been on the medication from three to six months, with some patients receiving Prantal Methylsulfate for over one year.

All of the seventy-six cases had bronchial asthma, sixty-nine had pollen or inhalant asthma, and seven infectious asthma. The ages of the patients, fifteen of whom were females and sixty-one, males, ranged from six to seventy-eight years. Distribution by age group was as shown in Table I.

Antihistamines had been tried previously in most of these patients for control of their symptoms with little or no success. The majority of them had had a variety of other commonly employed therapies with poor results. These drugs included theophylline, aminophylline, ephedrine, potassium iodide, belladonna and belladonna derivatives. Only temporary or limited beneficial results were obtained with any of these drugs, singly or in com-

bination. A large number had to stop the drugs because of unpleasant side actions: gastric distress; pain and regurgitation with aminophylline; excitement or urinary symptoms with belladonna and belladonna derivatives; skin rashes or salivary symptoms with potassium iodide.

TABLE I

No. Cases	Age Group
6	6 – 20 yrs.
35	21 – 30 "
20	31 – 40 "
15	41 and over
Total 76	

TABLE II

Prantal Methylsulfate 50 mg plus Chlor-Trimeton 4 mg, q.i.d.		Prantal Methylsulfate 50 mg, q.i.d.		All Cases	
No. Cases	Results	No. Cases	Results	No. Cases	Results
10	4 plus	25	4 plus	35	4 plus
5	3 plus	6	3 plus	11	3 plus
2	2 plus	9	2 plus	11	2 plus
3	1 plus	1	1 plus	4	1 plus
6	0	9	0	15	0
26		50		76	

Fifty patients were placed on a dosage regimen of Prantal Methylsulfate,* 50 mg four times daily. As some patients with bronchial asthma have been reported to respond favorably to Chlor-Trimeton,[1,9,12,16] it was decided to study a group of twenty-six patients on a regimen of Prantal Methylsulfate 50 mg plus Chlor-Trimeton* 4 mg four times daily.

All patients were examined at weekly intervals and carefully questioned to determine the degree of efficacy of therapy and evidence of drug side actions. An attempt was made to classify the degree of relief from asthmatic wheezing and cough as follows:

4 plus Complete freedom from all asthmatic symptoms.
3 plus Marked improvement in wheeze and cough.
2 plus Temporary improvement in wheeze and cough following drug ingestion.
1 plus Wheeze and cough present, but to a milder degree than before medication.
0 No improvement in wheeze or cough.

RESULTS

The results obtained in this study are tabulated (Table II) according to the above classification.

Fifty-seven patients (75 per cent) obtained complete or moderate relief of their wheezes and coughs. Most of them were able to sleep at night undisturbed by asthmatic symptoms. Their general physical well-being

*The Prantal Methylsulfate and Chlor-Trimeton Maleate tablets used in this study were supplied by the Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

was improved and all noted an improvement in appetite. Nineteen patients (25 per cent) noted little or no improvement with the drug alone or in combination. These nineteen patients, however, presented difficult problems in medical management. Six patients were markedly psychoneurotic. Four were undergoing active psychotherapy. Two had complicating pulmonary disease, one suffered from severe anthracosis and the other from bronchiectasis following pneumonia. Seven had a marked infectious type of asthma with mild or no pollen allergy and were given concomitant therapy with sulfonamides.

Prantal Methylsulfate reached its height of efficiency within one-half to one hour. A few patients who did not follow instructions to take the medication four times daily reported that a single dose was effective as long as twelve hours. Most patients, however, found it necessary to repeat the medication every four hours for sustained relief.

SIDE EFFECTS

Side effects were few. No symptoms of gastric irritation or cerebral stimulation were reported. Drowsiness did not occur with Prantal Methylsulfate alone or in combination with Chlor-Trimeton. Two patients complained of dryness of the nose and throat; one had marked anorexia and two experienced some dizziness of brief duration. One patient reported the occurrence of epistaxis following doses of Prantal Methylsulfate in excess of 50 mg. However, after a rest period, this patient tolerated Prantal Methylsulfate 50 mg q.i.d. without further episodes of epistaxis or other side actions.

DISCUSSION

Any new treatment for bronchial asthma is difficult to evaluate. Patients with this condition often respond well to sympathetic handling by the physician and are affected by his enthusiasm for the potential effectiveness of new drugs. We tried to eliminate the latter factor as much as possible by making no claims as to the effectiveness of the drug. Furthermore, most of these patients had been under our care for some time so that their patterns of response to the usual types of medication and general management were well known to us.

In this series, two-thirds of the patients received Prantal Methylsulfate alone and one-third received Prantal Methylsulfate plus Chlor-Trimeton. Prantal Methylsulfate alone appeared to be slightly more effective than the combination. However, due to the fact that many of these patients were known to be resistant to antihistamines and that this study was limited in the number of patients observed, it is believed that no conclusion can be drawn that the antihistamine interfered with the action of Prantal Methylsulfate. We believe that a larger series of cases not resistant to antihistamines would not show any significant difference in their response to Prantal Methylsulfate plus Chlor-Trimeton compared with Prantal Methylsulfate alone.

SUMMARY

Seventy-six patients with bronchial asthma have been treated with a new parasympathetic blocking agent, Prantal Methylsulfate, or a combination of Prantal Methylsulfate and Chlor-Trimeton. Seventy-five per cent of all patients treated were benefited by the medication. In 46 per cent, an excellent response was obtained with control of all symptoms. In 29 per cent, a good response was noted with partial control of symptoms. Poor or no response was noted in 25 per cent of the cases, most of which presented special problems in addition to bronchial asthma.

No lessening of the effectiveness of the drug has been observed during prolonged periods of treatment. No accumulation of side actions has been noted during the continuous use of the drug.

The high degree of effectiveness in relieving the symptoms of wheezing and coughing in bronchial asthma patients in this series indicates that Prantal Methylsulfate may act as a "medical vagotomy." In our opinion, Prantal Methylsulfate appears to offer a new approach to the bronchial asthma problem. These preliminary findings are presented with the hope that other allergists will conduct similar studies to appraise objectively the procedure reported herewith.

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A FOREIGN BODY IN THE RESPIRATORY TRACT WITH SYMPTOMS SIMULATING BRONCHIAL ASTHMA

ISIDOR BLACK, M.D., NATHAN RAVIN, M.D., and
MOSES L. FURMAN, M.D.
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A FOREIGN body in the bronchial tree simulating true bronchial asthma is noted infrequently, especially when *bilateral* wheezing is the only abnormal physical finding. The following case is presented because of its unusual history and the ultimate revelation of the etiology.

J. B., a nine-year-old girl, was seen in the pediatric clinic of the New York Flower and Fifth Avenue Hospital on August 2, 1948, complaining of a "deep chest cold" with coughing and wheezing of several months' duration. Physical examination revealed a well-nourished child weighing 79 pounds, with mild wheezing heard throughout both lungs accompanied by somewhat prolonged expiration. The temperature was 100.6 F. Examination of the nose and throat was negative. X-rays revealed clear nasal accessory sinuses and normal heart and pulmonary findings except for a fibro-calcific shadow in the second right interspace which was interpreted as a Ghon complex. The white blood count was 12,000; polymorphonuclears 59 per cent, eosinophiles 2 per cent, lymphocytes 39 per cent. A diagnosis of chronic bronchitis was made.

She was seen one week later, the cough and wheezing persisting, following which she was referred to the allergy clinic for diagnostic study and treatment.

On August 17, 1948, a history obtained in the allergy clinic revealed the fact that the patient was in and out of bed at the onset of her illness because of a recurrent cough and bouts of fever. Only after a month of these symptoms did the patient begin to wheeze and feel worse at night.

There was no history of sneezing, rhinorrhea, eczema, gastrointestinal upsets, nor any feeding problem in infancy. She had had a generalized urticaria following pyribenzamine hydrochloride orally which cleared up when this medication was discontinued. There was no family history of allergy.

The physical examination was negative except for bilateral wheezing and moderately prolonged expiration. Intradermal tests for foods and inhalants, including the relevant pollens and molds, were negative except for a slight reaction to house dust concentrate.

The patient made several more sporadic visits to the clinic, ten in all, between August 17, 1948, and March 15, 1949. She was treated with injections of house dust extract and a stock catarrhal vaccine, and received potassium iodide and ephedrine sulphate orally. At no time did she complain of dyspnea. The grandmother and patient variously reported partial or complete relief of symptoms, although wheezing could be heard upon examination of the chest at each visit. The otolaryngologist in the allergy clinic, an experienced bronchoscopist, reviewed the case on January 20, 1949, and, following his own examination, advised that the tonsils and adenoids be removed. This was not done.

The patient did not return to the clinic until March 15, 1949, at which time she brought with her the greater part of the shell of a pistachio nut which she had coughed up during the night. This incident was followed by immediate cessation of wheezing, and the examination at this time revealed a normal chest.

From the Dept. of Medicine (Allergy), New York Medical College, Flower-Fifth Avenue Hospital, New York, New York.

In view of this unusual turn of events, another chest x-ray was taken on March 17, 1949. The findings were the same as those reported in the first x-ray taken eight months previously, namely, the presence of a calcified Ghon tubercle in the right subclavicular region.

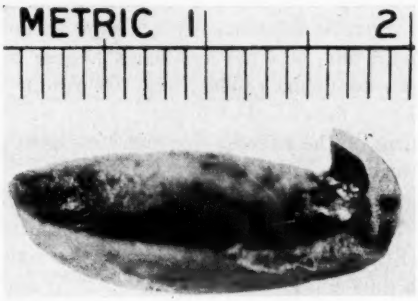

Fig. 1.

At this time, the grandmother offered an amended history stating that late in January, 1948, the girl swallowed or inhaled part of a nut shell which produced violent coughing for one hour. The following day the coughing reappeared and subsequently recurred on and off until it became constant. In the allergy clinic the patient had been attended by five doctors and no one had obtained a history implicating a foreign body.

The recovered pistachio nut shell was 10 mm long with ragged edges and hooked at one end (Fig. 1). It was undetermined where the shell had lodged since it was not visible on x-ray, nor was there any evidence of localized atelectasis or pneumonitis.

Re-examined one year later (March 1950), the patient remained symptom free and the chest revealed no abnormalities.

DISCUSSION

Most cases of asthma due to a foreign body in the tracheobronchial tree or in the esophagus have been reported mainly in the otolaryngological literature. Little space is given to the subject in textbooks of allergy.[1]

Chevalier Jackson[4] found that, in most instances, a foreign body in the pulmonary passages was misdiagnosed as tracheo-bronchitis, pneumonia or recurrent bronchitis. In 1,485 cases of foreign body in the air passages or esophagus an erroneous diagnosis of asthma was made forty-eight times. In some cases there was only an "asthmatoid" wheeze, but in others the simulation to bronchial asthma was so close that little criticism could be attached to the error in diagnosis. Reaction to a foreign body below the carina in both lung fields was uncommon except to particularly irritating substances. Nut kernels, nut shells, and corn lodged in a bronchus will frequently produce wheezing in both lung fields.

Lell[6] reported that in 176 children treated for bronchial asthma, eighteen had a foreign body in the respiratory tract and five had a foreign body in the esophagus.

When a foreign body in the air passages is suspected, fluoroscopy, performed within several hours after the incident has taken place, will show a flattened diaphragm with diminished excursion of the lung on the affected side. At the end of expiration, the heart and mediastinum will shift toward the uninvaded side. This is especially true when the foreign body is vegetable matter since vegetable substance is much more irritating than metallic articles. The invaded lung becomes less dense because of the trapped air and an obstructive emphysema results. This can readily be demonstrated by x-ray when taken at the end of expiration. Later, an obstructive atelectasis becomes evident on the affected side and a compensatory emphysema occurs on the normal side.

In this case there was an error in failing to consider a foreign body as a possible cause of the patient's complaints. A more accurate history should have been obtained from the grandmother who was obviously impatient and felt that too much time and effort was being spent in interrogation rather than examination and treatment. Furthermore, the negative findings on skin testing and x-ray examination of the chest and sinuses, as well as the negative family history, should have aroused suspicion and initiated further queries and studies.

SUMMARY

A foreign body, the shell of a pistachio nut, in the bronchial tree of a nine-year-old child resulted in a clinical picture simulating bronchial asthma, with persistent *bilateral* wheezing lasting more than a year. The correct diagnosis was made only after the patient coughed up the shell and the wheezing disappeared. There has been no recurrence of symptoms.

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EUROPA

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SUBLINGUAL TREATMENT OF BRONCHIAL ASTHMA WITH A POTENTIATED ISOPROPYL ARTERENOL PREPARATION

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RELIEF of the acute paroxysmal dyspnea so characteristic of bronchial asthma has long been, and continues to be, a real problem to the physician. A patient with bronchial asthma in an acute attack demands and must receive immediate and as complete as possible relief. One of the most effective treatments has been the parentral administration of epinephrine. To provide control for the patient with acute paroxysmal attacks of bronchial asthma, it has often been ncessary to instruct him in self-administration of epinephrine subcutaneously, which is frequently a serious disadvantage. Epinephrine has been used orally with unsatisfactory results. Ephedrine sulfate has been used orally and has often been found inadequate in the relief of acute attacks.

Within the last several years a new drug, isopropyl arterenol, has come into use in the United States. This compound, an analogue of epinephrine, is a potent bronchodilator and has been shown to be active both by inhalation and by sublingual use. Herxheimer,[3] in 1948, after reviewing the literature of the early Forties, studied the drugs in a series of patients with bronchial spasm and concluded: "Our experiments confirm the favorable published results. In isopropyl (arterenol) we possess a substance which has less effect on the circulation and more on the bronchial muscle than adrenaline, (and) can be given (sub)lingually instead of parenterally." He states that the sublingual dose of 20 to 30 mg is often inadequate to produce optimum effects and that the larger doses up to 60 mg carry more risk of side reaction.

Much of the published work in this country stresses the use of isopropyl arterenol by inhalation because, as Lowell et al[4] state, sublingual doses have not been very effective except in the high dose range. Franklin and Lowell[2] later wrote that absorption from the mouth is variable and incomplete, the usual sublingual dose being nearly fifty times that required subcutaneously.

In our experience with sublingual isopropyl arterenol, very little symptomatic effect was obtained with the recommended doses of 10 mg tablets sublingually, spaced at intervals of two to four hours. Alarming side effects, mainly, tachycardia, are very likely to occur if larger doses are used.

Herxheimer[3] reported that the aerosolized form of isopropyl arterenol could be potentiated by the addition of papaverine. A 1 per cent solution of papaverine combined with 1 per cent isopropyl arterenol often, in his series, produced the optimal effect usually obtained by 3 to 5 per cent

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solutions of isopropyl arterenol alone. Papaverine alone produced a minimal effect on the patients.

As it seems possible to potentiate the action of isopropyl arterenol when used by inhalation, it was postulated that its action by the sublingual route could be potentiated with a suitable antispasmodic drug. This drug must have the capacity to dilate the bronchioles by depression of the cholinergic nerves, and also counteract or reduce the cardiac action of isopropyl epinephrine. It must be active sublingually, must possess a minimum of side effects, and must be compatible both pharmaceutically and physiologically with isopropyl arterenol.

Of the many spasmodic drugs available, benzyl nicotinamide was selected for this study. This compound, synthesized by Bullman and Randall[1] in 1944, possesses marked antispasmodic properties, in common with a number of nicotinamide derivatives. Its pharmacology, reported by Suter,[5] indicated that it possessed the desired actions and its pharmaceutical properties proved excellent. Sublingual tablets containing 10 mg isopropyl arterenol and 100 mg benzyl nicotinamide were made available for study.*

Sixty patients with definitely established clinical diagnosis of bronchial asthma, ranging in age from four to seventy years, were selected for this study. Of these, forty-two (70 per cent) were chronically asthmatic, and eighteen (30 per cent) were acutely asthmatic.

The chronic asthmatic patients were given one tablet of isopropyl arterenol and benzyl nicotinamide sublingually three times daily. The shortest interval between any two doses was two hours. Acute asthmatic patients seen during acute attacks were given one tablet sublingually, repeated in two hours if needed. Patients seen in severe acute attacks not adequately relieved by the sublingual therapy were given epinephrine subcutaneously for more immediate relief.

RESULTS OF TREATMENT

A single tablet of benzyl nicotinamide and isopropyl arterenol used sublingually relieved the acute paroxysms in the chronic asthmatic patients in 85 per cent of the attacks. This relief as a rule appeared within ten minutes and lasted three to four hours. In all of these cases one tablet given three times daily was well tolerated and was sufficient to minimize the acute attacks in most of the patients. In no instance was a second tablet given sooner than two hours after the first.

The acute asthmatic patients were given the same treatment for their acute attacks. In 80 per cent of the attacks the symptoms were adequately relieved by the medication sublingually. It was interesting that the 20 per cent of the attacks not relieved by the sublingual medication were also very inadequately relieved by epinephrine subcutaneously.

*Supplied through the courtesy of the Medical Research Department, The National Drug Company, Philadelphia 4, Pa.

All of the patients in this series using the combination of benzyl nicotinamide and isopropyl arterenol had been on isopropyl arterenol alone previously with less adequate relief and very much more frequent complaint of side effects which were disagreeable to the patient.

The side effects with the use of the combined nicotinamide and isopropyl arterenol therapy were very much less and in no instance were severe enough to warrant withdrawal of the drug.

DISCUSSION

Isopropyl arterenol is a compound similar in structure to epinephrine, which was synthesized in an effort to find a substance with enhanced bronchodilating properties but without the marked cardiovascular effects of epinephrine. The bronchodilator effect of isopropyl arterenol has been shown to be greater than that of ephedrine, but the cardiac effect has not been overcome with the compound. Isopropyl arterenol has been a controversial drug since its introduction a few years ago. When used by inhalation, it is effective. When used sublingually, it is difficult to control the tachycardia caused by a dose sufficient to relieve the patient's symptoms. The addition of benzyl nicotinamide to the tablet of isopropyl arterenol for sublingual use is an effective and practical means of potentiating the relief and minimizing the side effects.

SUMMARY

Sixty patients with bronchial asthma who had previously received isopropyl arterenol sublingually for the relief of acute attacks were treated with the sublingual isopropyl arterenol in the same 10 mg dose with the addition of 100 mg benzyl nicotinamide in each of the sublingual tablets. A single tablet taken three times daily was effective in controlling 85 per cent of the acute paroxysms in forty-two chronically asthmatic patients. In eighteen acutely asthmatic patients, 80 per cent of the acute paroxysmal episodes were adequately relieved with the isopropyl arterenol-benzyl nicotinamide combination sublingually, in one tablet doses.

In the forty-two chronically asthmatic patients, a single tablet of the combination taken three times daily markedly reduced the frequency of acute paroxysmal attacks of asthma, and relieved the attacks when they occurred in 85 per cent of these cases.

In acute asthmatic episodes brought on as a result of acute upper respiratory infection, isopropyl arterenol with benzyl nicotinamide proved totally inadequate for lasting relief, as did epinephrine subcutaneously.

CONCLUSION

Benzyl nicotinamide when used in combination with isopropyl arterenol for sublingual therapy in bronchial asthma gives a definite potentiation of

the relief of the bronchospasm, and at the same time gives a marked decrease in the incidence and severity of tachycardia and other side effects seen with isopropyl arterenol alone in sufficient doses to affect the bronchospasm.

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ANTIMICROBIAL AGENTS IN TUBERCULOSIS

Antimicrobial agents are "indispensable" in the treatment of tuberculosis, but should be combined with other appropriate forms of treatment, such as rest, collapse therapy, and surgical procedures, according to the Committee on Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

A statement by the committee, published in the August, 1952, issue of the *American Review of Tuberculosis,* supplements one issued in 1951. It calls the combination of streptomycin or its derivative, dihydrostreptomycin, and PAS "the most effective drug for the treatment of tuberculosis."

Regarding isoniazid (isonicotinic acid hydrazide), the new drug being tried in tuberculosis treatment, the report, drafted at a meeting of the committee in May, 1952, says that "preliminary studies suggest that isoniazid and its isopropyl derivative are potent antituberculosis agents, particularly valuable in the treatment of patients with tubercle bacilli which are highly resistant to streptomycin." Further study is needed, however, according to the report, to determine the value of the drug in such cases and also in patients with tubercle bacilli still sensitive to streptomycin.

Pyrazinamide (aldinamide), another new drug, is effective against the tubercle bacillus in the test tube and in experimental animals, according to the committee, and preliminary reports of clinical studies suggest that it is effective in treating patients with tuberculosis. However, tubercle bacilli resistant to the drug rapidly appear, thus limiting the period of usefulness of the drug. Further studies now under way, the report continues, should determine whether clinical use of the drug is warranted.

Further studies were also recommended to determine the usefulness of terramycin and viomycin in tuberculosis treatment.

Preliminary Program

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

April 24-26, 1953

and

NINTH ANNUAL CONGRESS

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Standardization (including sub-committees for Certification of Allergenic Extracts and Standardization of Aerosol Therapy	9:00 a.m.	Room 3
Pollen	9:00 a.m.	Room 6
Public Education	10:00 a.m.	Room 3
Pediatric Allergy	10:00 a.m.	Room 6
Finance	11:00 a.m.	Room 3
Psychosomatic Allergy	11:00 a.m.	Room 6
Editorial Board	2:00 p.m.	Room 3
Rheumatism and Arthritis	2:00 p.m.	Room 6
Program	3:00 p.m.	Room 9
Aerobiology	3:00 p.m.	Room 6
By Laws	4:00 p.m.	Room 9
New and Unused Therapeutics	4:00 p.m.	Room 6
Sunday, April 26		
Board of Directors	9:00 a.m.	Room 8
Board of Regents	10:00 a.m.	Room 8
The American Association for Mycological Investigation	2:00 p.m.	Room posted later
Monday, April 27		
Dermatology	7:30 p.m.	North Assembly Room
Wednesday, April 29		
New Board of Regents	8:30 a.m.	Room 8

J. Warrick Thomas, M.D.
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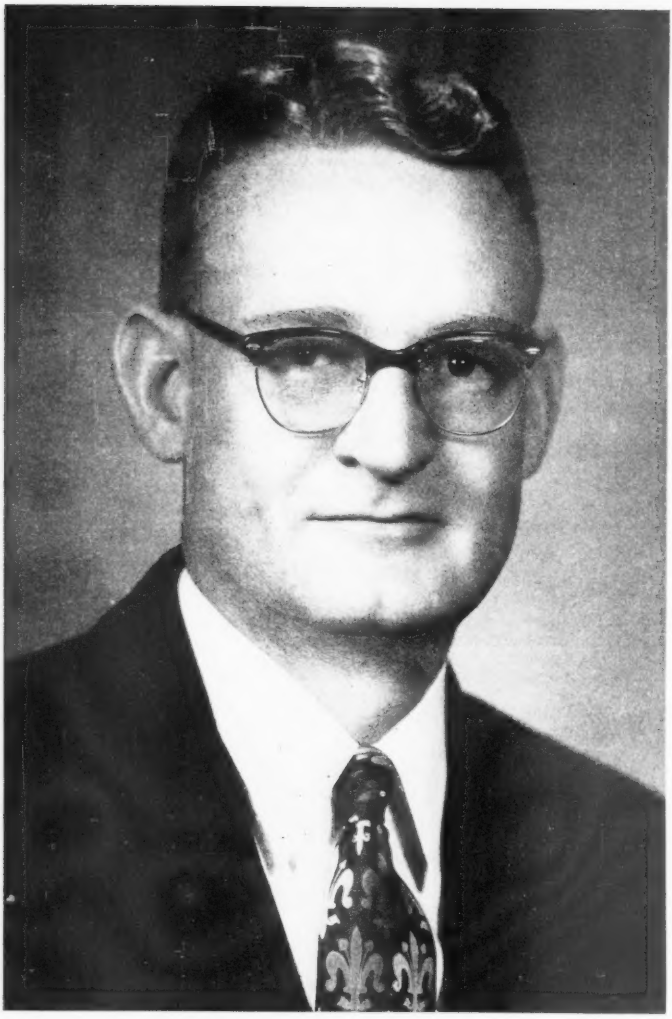

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Richmond, Virginia

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Graduate Instructional Course in Allergy

(Preliminary program; subject to minor changes)

FRIDAY, APRIL 24, 1953

Morning Session — North Ball Room

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Chairman: J. Warrick Thomas, M.D., Richmond, Virginia

8:00- 9:00 **Registration**

9:00- 9:30 **Botany of Pollenosis**

Oren C. Durham, M.D.,* Chief Botanist, Abbott Laboratories; Special Lecturer in Allergy, Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois

9:30-10:15 **Physiologic Mechanism of Allergy**

Bret Ratner, M.D., Professor of Clinical Pediatrics (Allergy) and Associate Professor of Immunology, New York Medical College; Attending Pediatrician, Flower and Fifth Avenue Hospitals; Director of Pediatrics, Sea View Hospital, New York, New York

10:20-11:00 **Pathology of Allergy**

Milton G. Bohrod, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

11:05-11:45 **Etiology of Allergy**

Cecil M. Kohn, M.D., Kansas City, Missouri

11:45-12:30 **Diagnosis and Tests Used in Allergy**

M. Murray Peshkin, M.D., New York, New York

ROUND TABLE LUNCHEONS

Chairman: Leon Unger, M.D., Chicago, Illinois

Co-Chairman: Morris A. Kaplan, M.D., Chicago, Illinois

Friday, April 24

12:30- 2:00 A-1 **Preparation of Extracts—Room 1**

Morris A. Kaplan, M.D., Assistant Professor of Medicine, Chicago Medical School; Attending Assistant, Michael Reese Hospital; Attending Allergist, Mandel Clinics, Michael Reese Hospital, Chicago, Illinois

Stephen D. Lockey, M.D., Allergist, Lancaster General Hospital, Lancaster, Pennsylvania

George E. Rockwell, M.D., Milford, Ohio, Attending Physician, Bethesda Hospital and Our Lady of Mercy Hospital, Cincinnati, Ohio

12:30- 2:00 A-2 **Skin Tests (Techniques, Values, Fallacies)—Room 2**

Norman J. Ehrlich, M.D., Chicago, Illinois

M. Murray Peshkin, M.D., New York, New York

Boen Swinny, M.D., Consultant in Allergy, Brooke General Hospital, United States Army, Ft. Sam Houston, Texas; Instructor in Allergy, Clinical Faculty, University of Texas; Instructor in Allergy, Clinical Faculty, Baylor University, San Antonio, Texas

*By invitation

12:30- 2:00 A-3 **Bacterial Allergy—Room 4**
HERMANN BLATT, M.D., Cincinnati, Ohio
ISADORE PILOT, M.D., Chicago, Illinois
MAX SAMTER, M.D.,* Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois

12:30- 2:00 A-4 **Food Allergy—Room 9**
HARRY S. BERNTON, M.D., Clinical Professor of Medicine, Howard University; Clinical Specialist in Allergy, Allergens Research Division, U. S. Department of Agriculture; Allergist to Providence Hospital; Allergist to Freedman Hospital, Washington, D. C.
ORVAL R. WITHERS, M.D., Kansas City, Missouri, Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence and Kansas City, Kansas
MICHAEL ZELLER, M.D., Clinical Instructor in Medicine, University of Illinois College of Medicine, Chicago, Illinois

12:30- 2:00 A-5 **Role of Fungi in Respiratory Allergy—Room 10**
CLIFFORD H. KALB, M.D., Milwaukee, Wisconsin
HOMER E. PRINCE, M.D., Professor of Clinical Medicine, Baylor University College of Medicine, Houston, Texas
A. M. TARGOW, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine; Attending Physician, Los Angeles County General Hospital, Los Angeles, California

FRIDAY, APRIL 24, 1953

Afternoon Session — North Ball Room

Bronchial Asthma and Related Heart and Lung Conditions

Chairman: LEON UNGER, M.D., Chicago, Illinois

2:00- 2:45 **Pathophysiology of Bronchial Asthma and Emphysema, With Functional Tests**
MAURICE S. SEGAL, M.D., Clinical Professor of Medicine, Tufts College Medical School, and Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts

2:45- 3:25 **Diagnosis of Bronchial Asthma**
HAL M. DAVISON, M.D., Chief of Medicine and Instructor in Allergy, Georgia Baptist Hospital, Atlanta, Georgia

3:30- 4:10 **Treatment of Bronchial Asthma**
LEON UNGER, M.D., Northwestern University Medical School and University of Illinois School of Medicine, Chicago, Illinois

4:15- 4:55 **Differential Diagnosis from Cardiovascular Conditions**
MISCHA J. LUSTOK, M.D.,* Assistant Clinical Professor of Medicine, Cardiovascular Department, Marquette University School of Medicine, Milwaukee, Wisconsin

5:00- 5:40 **Differential Diagnosis from Other Pulmonary Conditions**
MEYER R. LICHENSTEIN, M.D., Clinical Assistant Professor of Medicine (Allergy), University of Illinois School of Medicine, Chicago, Illinois

FRIDAY, APRIL 24, 1953

Evening Session — North Ball Room

Chairman: HAL M. DAVISON, M.D., Atlanta, Georgia

8:00- 8:35 **Bronchoscopic Clinic (Movie) with Differential Diagnosis of Wheezing**
PAUL H. HOLINGER, M.D.,* and KENNETH C. JOHNSTON, M.D.,* Chicago, Illinois

*By invitation

8:40-10:00 **Practical Management of Allergic Patients**

(A) Nasal Allergy
HARRY L. ROGERS, M.D., Chief of Allergy Clinic, Out Patient Department, Jefferson Hospital; Chief of Allergy Clinic, Cooper Hospital, Camden, New Jersey; Assistant in Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

(B) Bronchial Asthma
HAL M. DAVISON, M.D., Chief of Medicine and Instructor in Allergy, Georgia Baptist Hospital, Atlanta, Georgia

(C) Pediatric Allergy
SAMUEL J. LEVIN, M.D., Instructor in Clinical Pediatrics, Wayne University College of Medicine; Attending Allergist, Children's Hospital of Michigan, and Director of the Allergy Clinic; Attending Allergist, Woman's Hospital, Detroit, Michigan

(D) Dermatologic Allergy
GEORGE L. WALDBOTT, M.D., Detroit, Michigan

(E) Food Allergy
ORVAL R. WITHERS, M.D., Kansas City, Missouri, Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence and Kansas City, Kansas

(Each speaker limited to 10 minutes, followed by questions and answers)

SATURDAY, APRIL 25, 1953

Morning Session — North Ball Room

Allergy of Eye, Ear, Nose

Chairman: HARRY S. BERNTON, M.D., Washington, D. C.

9:00- 9:30 **History of Allergy**
ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School; Physician-in-chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts

9:30-10:00 **Classification and Occurrence of Molds**
NATHAN SCHAFFER, M.D., Chief of Allergy, Orange Memorial Hospital, East Orange, New Jersey

10:05-10:30 **Classification and Occurrence of Smuts, Rusts, Yeasts, Grain Mill Dust**
FRED W. WITTICH, M.D., President, International Association of Allergology, Minneapolis, Minnesota

10:30-11:00 **Diagnosis of Nasal Allergy**
HARRY S. BERNTON, M.D., Clinical Professor of Medicine, Howard University; Clinical Specialist in Allergy, Allergens Research Division, U. S. Department of Agriculture; Allergist to Providence Hospital; Allergist to Freedman Hospital, Washington, D. C.

11:05-11:35 **Treatment of Nasal Allergy**
MORRIS A. KAPLAN, M.D., Assistant Professor of Medicine, Chicago Medical School; Attending Assistant, Michael Reese Hospital; Attending Allergist, Mandel Clinics, Michael Reese Hospital, Chicago, Illinois

11:35-12:00 **Allergy of the Eye**
SAMUEL J. TAUB, M.D.,* Professor of Medicine and Chief, Department of Allergy, Chicago Medical School, Chicago, Illinois

12:00-12:30 **Allergy of the Ear**
GEORGE E. SHAMBAUGH, JR., M.D., Associate Professor of Otolaryngology, Northwestern University Medical School, Chicago, Illinois

*By invitation

ROUND TABLE LUNCHEONS

Saturday, April 25

12:30- 2:00 B-1 Bronchial Asthma—Room 1

VINCENT J. DERBES, M.D., Associate Professor of Medicine and Director of Allergy Division, Department of Internal Medicine, Tulane University School of Medicine; Head of Allergy Department, Ochsner Clinic; Consultant in Allergy, U. S. Marine Hospital, New Orleans, Louisiana

MAYER A. GREEN, M.D., Director of the Department of Allergy, Columbia Hospital, Pittsburgh, Pennsylvania

MAURICE S. SEGAL, M.D., Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts

12:30- 2:00 B-2 Nasal Allergy—Room 2

HUGH A. KUHN, M.D., Hammond, Indiana
A. L. MAIETTA, M.D., Chief of the Allergy Clinic, Carney Hospital, Boston, Massachusetts

NATHAN E. SILBERT, M.D., Chief of Allergy, Captain John Adams Hospital, Lawrence Quigley Memorial Hospital and Soldiers' Home, Chelsea, Massachusetts; Consultant in Allergy, Danvers State Hospital, Danvers, Massachusetts; Saugus General Hospital, Saugus, Massachusetts; and Union Hospital, Lynn, Massachusetts

12:30- 2:00 B-3 Cerebral Allergy—Room 4

ALEX J. ARIEFF, M.D.,* Chicago, Illinois
HAL M. DAVISON, M.D., Chief of Medicine and Instructor in Allergy, Georgia Baptist Hospital, Atlanta, Georgia

ALBERT H. UNGER, M.D., Clinical Assistant, Northwestern University Medical School; Attending Staff, Columbus Hospital, Chicago, Illinois

12:30- 2:00 B-4 Psychosomatic Factors in Allergy—Room 9

BENNETT KRAFT, M.D., Lecturer in Allergy, Indianapolis General Hospital; Lecturer in Psychosomatic Medicine, Indiana University School of Medicine, Indianapolis, Indiana.

WILLIAM KAUFMAN, PH.D., M.D., Bridgeport, Connecticut

JAMES A. MANSMANN, M.D., Assistant Professor of Medicine, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

12:30- 2:00 B-5 Food Allergy—Room 10

CLARENCE S. BUCHER, M.D., Staff Member, Burnham City Hospital, Champaign, Illinois

PHILIP M. GOTTLIEB, M.D., Instructor in Medicine, University of Pennsylvania; Chief of Allergy, Kensington Hospital; Associate Allergist, Jewish Hospital; Allergist, Sidney Hillman Medical Center, Philadelphia, Pennsylvania

THERON G. RANDOLPH, M.D., Chicago, Illinois

*By invitation

SATURDAY, APRIL 25, 1953

Afternoon Session — North Ball Room

Dermatologic Allergy

Chairman: ADOLPH ROSTENBERG, JR., M.D., Chicago, Illinois

2:00- 2:20 Fundamentals of Dermatologic Allergy
ADOLPH ROSTENBERG, JR., M.D., Associate Professor of Dermatology and Associate Director of the Allergy Unit, Illinois College of Medicine, Chicago, Illinois

2:20- 2:50 Contact Dermatitis
GEORGE L. WALDBOTT, M.D., Detroit, Michigan

2:50- 3:20 Eczema in Adults
STEPHEN ROTHMAN, M.D., Professor of Dermatology and Syphilology and Head of the Section, School of Medicine, University of Chicago, Chicago, Illinois

3:25- 3:55 Drug Eruptions
ADOLPH ROSTENBERG, JR., M.D., Associate Professor of Dermatology and Associate Director of the Allergy Unit, Illinois College of Medicine, Chicago, Illinois

3:55- 4:25 Urticaria, Angioneurotic Edema, Related Skin Conditions
JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

4:30- 5:00 Dermo-Fungous Allergy
HAROLD G. RAVITS, M.D., Saint Paul, Minnesota, Clinical Instructor of Dermatology, University of Minnesota, Minneapolis, Minnesota

5:00- 5:30 Local Therapy in Dermatologic Allergy
JAMES R. WEBSTER, M.D.,* Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

SATURDAY, APRIL 25, 1953

Evening Session — North Ball Room

Chairman: ETHAN ALLAN BROWN, M.D., Boston, Massachusetts

8:00- 8:30 Collagen Diseases
MILTON G. BOHROD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

8:30-10:00 Symposium on ACTH and Cortisone in Allergic Diseases

(A) Anatomy and Physiology of the Adrenal and Pituitary Glands
RACHMIEL LEVINE, M.D.,* Professorial Lecturer in the Department of Physiology, University of Chicago; Director of Department of Metabolic and Endocrine Research, Michael Reese Hospital, Medical Research Institute, Chicago, Illinois

(B) Biochemical Aspects of ACTH and Cortisone
SMITH FREEMAN, M.D.,* Professor of Experimental Medicine, Northwestern University Medical School, Chicago, Illinois

(C) Clinical Aspects
ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School: Physician-in-chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts

(Each speaker limited to 20 minutes, followed by questions and answers)

*By invitation

SUNDAY, APRIL 26, 1953

Morning Session — North Ball Room

Pediatric Allergy

Chairman: BRET RATNER, M.D., New York, New York

9:00- 9:30 Growth and Development of the Allergic Child
NORMAN W. CLEIN, M.D. Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington

9:30-10:15 Food Allergy
BRET RATNER, M.D., Professor of Clinical Pediatrics (Allergy) and Associate Professor of Immunology, New York Medical College; Attending Pediatrician, Flower and Fifth Avenue Hospitals; Director of Pediatrics, Sea View Hospital, New York, New York

10:15-11:00 Eczema (Atopic Dermatitis) in Childhood
JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-chief, Genesee Hospital, Rochester, New York

11:00-11:30 Respiratory Allergy in Children
SAMUEL J. LEVIN, M.D., Instructor in Pediatrics, Wayne University College of Medicine, Detroit, Michigan

11:30-12:00 Serum Sickness
RALPH SPAETH, M.D.,* Assistant Professor of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois

12:00-12:30 Psychodynamics in Childhood Allergy
HYMAN MILLER, M.D., Beverly Hills, California, Associate Clinical Professor of Medicine, University of California at Los Angeles Medical School, Los Angeles, California

ROUND TABLE LUNCHEONS

Sunday, April 26

12:30- 2:00 C-1 Dermatologic Allergy—Room 1
KENNETH A. BAIRD, M.D., West St. John, N. B., Canada
SIDNEY FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan
GEORGE L. WALDBOTT, M.D., Detroit, Michigan

12:30- 2:00 C-2 Pediatric Allergy—Room 2
ETHEL M. DAVIS, M.D., Resident Instructor of Juvenile Research; Attending Pediatrician Michael Reese Hospital; Director of Children's Allergy Clinic and Consultant in Allergy, Cook County Children's Hospital, Chicago, Illinois
WALKER L. RUCKS, M.D., Assistant Professor of Pediatrics, University of Tennessee; Consultant, Baptist Memorial Hospital; Pediatrics and Pediatric Allergy, University of Tennessee, Memphis, Tennessee
FREDERIC SPEER, M.D., Department of Pediatrics, University of Kansas, Kansas City, Kansas

12:30- 2:00 C-3 Bronchial Asthma—Room 4
GILES A. KOELSCHE, M.D., Consultant, Division of Medicine, Mayo Clinic, Rochester, Minnesota
JAMES E. STROH, M.D., Clinical Assistant Professor of Medicine, University of Washington, Seattle, Washington
G. ESTRADA DE LA RIVA, M.D., Havana, Cuba.

*By invitation

12:30- 2:00 C-4 **ACTH and Cortisone in Allergy—Room 9**

NOAH D. FABRICANT, M.D.,* Chicago, Illinois

JONATHAN FORMAN, M.D., Worthington, Ohio

IRVING W. SCHILLER, M.D.,* Associate Staff, Beth Israel Hospital; Physician, Allergy Clinic, Massachusetts Memorial Hospital; Assistant Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts

12:30- 2:00 C-5 **Respiratory Allergy Due to Occupational Exposure—Room 10**

LEON UNGER, M.D., Northwestern University Medical School and University of Illinois School of Medicine, Chicago, Illinois

S. H. JAROS, M.D., Tuckahoe, New York, Chief, Allergy Clinic, Division of Internal Medicine, Grasslands Hospital, Valhalla, New York.

FRED W. WITTICH, M.D., President, International Association of Allergology, Minneapolis, Minnesota

SUNDAY, APRIL 26, 1953

Afternoon Session — North Ball Room

Chairman: HARRY L. ROGERS, M.D., Philadelphia, Pennsylvania

2:00- 2:40 **Drug Allergies**

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School; Physician-in-chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts

2:45- 3:25 **Allergic Headaches, Including Migraine**

ALBERT H. UNGER, M.D., Clinical Assistant, Northwestern University Medical School; Attending Staff, Columbus Hospital, Chicago, Illinois

3:25- 3:55 **Allergy in the Abdomen**

HERMAN A. LEVY, M.D., Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois

4:00- 4:30 **Miscellaneous Allergies**

LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

4:30- 5:15 **Psychodynamics in Adult Allergies**

HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

SUNDAY, APRIL 26, 1953

Evening Seminars

8:00-10:00 **EMOTIONAL FACTORS IN ALLERGIC DISORDERS**

Demonstration and discussion of actual procedures used in diagnosis and treatment

Room No. 3 **Tape Recordings of Interviews with Allergic Patients**

Clinician: JOHN H. MITCHELL, M.D., Associate Professor, Department of Medicine, Ohio State University, Columbus, Ohio
Reporter: BENNETT KRAFT, M.D., Lecturer in Allergy, Indianapolis General Hospital; Lecturer in Psychosomatic Medicine, Indiana University School of Medicine, Indianapolis, Indiana

*By invitation

Room No. 4 Psychoanalytically Oriented Interviews

Clinician: HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

Reporter: WILLIAM KAUFMAN, PH.D., M.D., Bridgeport, Connecticut

Room No. 5 An Actual Interview with Parents of an Allergic Child

Clinician: HYMAN MILLER, M.D., Beverly Hills, California, Associate Clinical Professor of Medicine, University of California at Los Angeles Medical School, Los Angeles, California

Reporter: BOEN SWINNY, M.D., Consultant in Allergy, Brooke General Hospital, United States Army, Ft. Sam Houston, Texas; Instructor in Allergy, Clinical Faculty, University of Texas; Instructor in Allergy, Clinical Faculty, Baylor University, San Antonio, Texas

Room No. 6 An Actual Diagnostic Play Session with an Allergic Child

Clinician: DOROTHY W. BARUCH, PH.D.,* Beverly Hills, California

Reporter: HAL M. DAVISON, M.D., Chief of Medicine and Instructor in Allergy, Georgia Baptist Hospital, Atlanta, Georgia

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Each group is limited to 30 registrants, and it may be necessary to assign some to groups other than their choice.

Attendance for the Monday evening summaries of the Seminars is unlimited.

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Fee for the Instructional Course is $50 which includes three round table luncheons.

*By invitation

TECHNICAL EXHIBITS

During the mid-morning and mid-afternoon of each of the three days of the Scientific Program, it is imperative that a half-hour be allotted for visiting the exhibits. The chairman of each section is instructed to call a recess at this time, and participants have received printed instructions from the Overall Chairman to prepare their papers so as to adhere to the time limits.

We are obligated by contract to extend this courtesy to our exhibitors. If it were not for them, it would be impossible to finance annually a successful program on an extensive scale. You will find this year's Technical Exhibits extraordinary, and worthy of your time. The representatives will be pleased to receive any suggestions or comments you may make. Many of these exhibitors are advertisers in the ANNALS OF ALLERGY, and/or Sustaining Members of the College.

Your co-operation in showing our appreciation to the Technical Exhibitors is earnestly requested.

Ninth Annual Congress

(Preliminary program; subject to minor changes)

SUNDAY, APRIL 26, 1953

2:00- 5:30 **Registration—The Foyer**

2:00- 4:00 **Meeting of the members of The American Association for Mycological Investigation**
HOMER E. PRINCE, M.D., *President*

8:00-10:00 **Emotional Factors in Allergic Disorders**
Four Clinical Seminars. (See details previous page)

MONDAY, APRIL 27, 1953

Morning Session — Grand Ball Room

GENERAL SESSION

Chairman: GILES A. KOELSCHE, M.D., Rochester, Minnesota

9:00- 9:10 **Viability of Leukocytes as a Test for Specific Bacterial Allergy**
HERMANN BLATT, M.D., Cincinnati, Ohio

9:15- 9:25 **Does Smoking Harm the Allergic Patient?**
HENRY D. OGDEN, M.D., Assistant Professor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

9:35- 9:45 **Respiratory and Physical Exercise in the Treatment of Bronchial Asthma**
BERNARD T. FEIN, M.D., Chief, Allergy Clinic, Veterans Administration Regional Office, San Antonio, Texas

9:55-10:25 **Microscopic Observations of the Intrahepatic Circulation of Living Guinea Pigs Before and During Anaphylaxis**
WALTER S. BURRAGE, M.D.,* Associate Physician and Head of Allergy Clinic, Massachusetts General Hospital, Boston, Massachusetts; Instructor in Medicine, Harvard University, Cambridge, Massachusetts; President, American Academy of Allergy

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There will be a short discussion following each paper

10:30-11:00 **RECESS TO VISIT EXHIBITS**

11:00-11:25 **The Problem of Respiratory Acidosis in Chronic Pulmonary Emphysema**
MAURICE S. SEGAL, M.D., Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts

11:35-11:45 **On the Value of Piromen in the Treatment of Allergic Disorders**
D. EDWARD FRANK, M.D., Sun Valley, California
WALTER R. MACLAREN, M.D., Pasadena, California

11:50-12:00 **Food-Induced, Allergic Musculoskeletal Syndromes**
WILLIAM KAUFMAN, PH.D., M.D., Bridgeport, Connecticut

*By invitation

12:05-12:15 **Sensitivity to Pine, Petroleum, Coal-tar and Derivatives**

THERON G. RANDOLPH, M.D., Chicago, Illinois

12:20-12:30 **Allergic Parotitis**

BOEN SWINNY, M.D., Consultant in Allergy, Brooke General Hospital, United States Army, Ft. Sam Houston, Texas; Instructor in Allergy, Clinical Faculty, University of Texas; Instructor in Allergy, Clinical Faculty, Baylor University, San Antonio, Texas

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There will be a short discussion following each paper.

12:30- 2:00 **LUNCH**

MONDAY, APRIL 27, 1953

Afternoon Session — Grand Ball Room

GENERAL SESSION

Chairman: HENRY D. OGDEN, M.D., New Orleans, Louisiana

2:00- 2:10 **The Dentist in Allergic Diagnosis**

IRVIN SUSSMAN, M.D., Bridgeton, New Jersey, Associate, Division of Internal Medicine, Hahnemann Medical College; Attending Physician, Hahnemann Hospital, Philadelphia, Pennsylvania; Chief of Internal Medicine, Elmer Community Hospital, Elmer, New Jersey; Consultant in Internal Medicine and Cardiology, Millville Hospital, Millville, New Jersey

2:15- 2:45 **Bronchial Insufficiency**

EDWIN R. LEVINE, M.D.,* Attending Physician, Cook County Hospital, Chicago, Illinois

2:50- 3:00 **Twenty-two Years' Experience in the Treatment of Allergy with Anterior Pituitary Extract**

CLARENCE S. BUCHER, M.D., Staff Member, Burnham City Hospital, Champaign, Illinois

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There will be a short discussion following each paper.

3:00- 3:30 **RECESS TO VISIT EXHIBITS**

3:30- 3:45 **Preliminary Study of Radio-active Ragweed Pollen**

GEORGE V. LEROY, M.D.,* Associate Professor, Department of Medicine, The University of Chicago, Chicago, Illinois

3:55- 4:10 **Emergencies in the Allergist's Office**

GEORGE L. WALDBOTT, M.D., Detroit, Michigan

4:20- 4:45 **Allergic Dermatoses in Industry: Their Diagnosis and Treatment**

RAYMOND R. SUSKIND, M.D.,* Associate Professor, Department of Preventive Medicine and Industrial Health; Assistant Professor of Dermatology and Syphilology, College of Medicine, University of Cincinnati, Cincinnati, Ohio

4:55- 5:05 **Hypoallergic Penicillin. V. (Pyribenzamine-Penicillin). Comparison of Results and Final Conclusions from all Studies**

S. WILLIAM SIMON, M.D., Chief, Allergy Clinic, Brown General Hospital, Veterans Administration Center, Dayton, Ohio

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There will be a short discussion following each paper.

*By invitation

5:10- 5:25 **Aerosol Trypsin Therapy in the Treatment of Asthma**

HOMER E. PRINCE, M.D., Professor in Medicine, Baylor University College of Medicine; Chief of Allergy, Hermann Hospital, Houston, Texas

RICHARD L. ETTER, M.D., Instructor in Clinical Medicine, Baylor University College of Medicine; Associate in Allergy, Hermann Hospital, Houston, Texas

5:25- 5:35 **The Use of Tryptar (Trypsin) in Bronchial Asthma and Other Respiratory Conditions**

LEON UNGER, M.D., Attending Physician, Wesley Memorial Hospital; Associate Professor, Northwestern University Medical School, Chicago, Illinois

ROBERT R. LEE, M.D.,* Attendant, Department of Anesthesia, Wesley Memorial Hospital, Chicago, Illinois

5:35- 5:45 **Discussion of papers by Doctors Prince and Unger.**

MONDAY, APRIL 27, 1953

Evening Session — North Assembly Room

7:30-10:00 **DERMATOLOGIC ALLERGY**

Chairman: STEPHAN EPSTEIN, M.D., Marshfield, Wisconsin

Co-Chairman: ALEX S. FRIEDLAENDER, M.D., Detroit, Michigan

Discussion of Committee Matters
(short business meeting)
Dermatologic Committee members

Diagnosis of Nonallergic Skin Diseases
ADOLPH B. LOVEMAN, M.D., Assistant Clinical Professor of Dermatology and Syphilology, University of Louisville School of Medicine, Louisville, Kentucky

General Management of Dermatitis
ROBERT R. KIERLAND, M.D.,* Consultant, Section on Dermatology, Mayo Clinic, Rochester, Minnesota; Associate Professor of Dermatology in the Mayo Foundation Graduate School, University of Minnesota, Minneapolis, Minnesota

Round Table Discussion—Dermatologic Allergy
STEPHAN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin; Clinical Associate Professor of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota

RUDOLF L. BAER, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York

ALEX FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan

ADOLPH B. LOVEMAN, M.D., Assistant Clinical Professor of Dermatology and Syphilology, University of Louisville School of Medicine, Louisville, Kentucky

ADOLPH ROSTENBERG, JR., M.D., Associate Professor of Dermatology and Associate Director of the Allergy Unit, Illinois College of Medicine, Chicago, Illinois

STEPHEN ROTHMAN, M.D., Professor of Dermatology and Syphilology and Head of the Section, School of Medicine, University of Chicago, Chicago, Illinois

ROBERT R. KIERLAND, M.D.,* Consultant, Section on Dermatology, Mayo Clinic, Rochester, Minnesota; Associate Professor of Dermatology in the Mayo Foundation Graduate School, University of Minnesota, Minneapolis, Minnesota

*By invitation

MONDAY, APRIL 27, 1953

Evening Session — North Ball Room

8:00-10:00 CLINICAL PANEL ON PSYCHOSOMATIC ALLERGY

Moderator: HYMAN MILLER, M.D., Beverly Hills, California

The clinicians and reporters from each seminar of the previous evening on EMOTIONAL FACTORS IN ALLERGIC DISORDERS, will summarize their findings.

Procedure:

1. Brief summaries on what was seen and heard at the seminars, as well as the conclusions of the group in regard to the application of this information to private practice.
2. Questions to members of the panel, and comments and discussion from the floor.
3. Trends in the practice of allergy as indicated by answers to the questionnaire "How Do You Feel About Feelings?" summarized by M. MURRAY PESHKIN, M.D., New York, New York

TUESDAY, APRIL 28, 1953

Morning Session — Grand Ball Room

Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

9:00- 9:20 Presidential Address

J. WARRICK THOMAS, M.D., Assistant Professor, Clinical Medicine, Medical College of Virginia, Richmond, Virginia

9:20- 9:25 Introduction of M. Murray Peshkin, M.D., President-Elect

9:25-10:00 Direct Observations on Human Allergic Cells with Tissue Culture Technique

C. M. POMERAT

Guest Speaker

C. M. POMERAT, Ph.D., Professor of Cytology, The University of Texas, Medical Branch, Galveston, Texas

10:00-10:30 RECESS TO VISIT EXHIBITS

10:30 Business Meeting

12:30- 2:00 LUNCH

12:30- 2:00 ROUND TABLE LUNCHEON—Pediatric Allergy—North Assembly Room

Moderator: JEROME GLASER, M.D., Rochester, New York

Significance of Eosinophiles in the Stools in the Diagnosis of Gastrointestinal Allergy in Pediatric Practice

ARTHUR H. ROSENBLUM, M.D.,* Attending Pediatrician, Cook County Hospital; Assistant Attending Pediatrician, Sarah Morris Hospital; Associate in Pediatrics, Northwestern University Medical School, Chicago, Illinois

*By invitation

Gastrointestinal Allergy and the Celiac Syndrome

RALPH H. KUNSTADTER, M.D.,* Attending Pediatrician, Michael Reese Hospital; Chief, Children's Endocrine Clinic, Michael Reese Hospital, Chicago, Illinois

Immunization Against Tetanus by Means of Toxoid and its Importance in Pediatric Allergy

RALPH SPAETH, M.D.,* Assistant Professor of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois

Drug Allergy in Infancy and Childhood

MAXIMILIAN BERKOWITZ, M.D.,* Department of Pediatrics, Government Hospital, Haifa, Israel; Visiting Fellow in Pediatric Allergy, Clinic of Jerome Glaser, Rochester, New York

TUESDAY, APRIL 28, 1953

Afternoon Session — Grand Ball Room

SECTION ON PEDIATRIC ALLERGY

Chairman: BRET RATNER, M.D., New York, New York

Co-Chairman: JEROME GLASER, M.D., Rochester, New York

2:00- 2:10 **Personality Changes Induced in Children by the Use of Certain Antihistaminic Drugs**

NATHAN SCHAFFER, M.D., Chief of Allergy, Orange Memorial Hospital, East Orange, New Jersey

2:20- 2:35 **Asthma in Infancy**

WILLIAM P. BUFFUM, M.D., Chairman, Sub-Board of Allergy, American Board of Pediatrics; Physician-in-chief, Pediatric Service, Rhode Island Hospital, Providence, Rhode Island

2:45- 3:00 **Relationship of Foods to Asthma**

HAROLD I. LECKS, M.D.,* Assistant Allergist, Children's Hospital; Instructor in Pediatrics, University of Pennsylvania Medical School, Philadelphia, Pennsylvania

3:10- 3:30 **Value of Vaccines in Respiratory Allergy of Children**

ALBERT V. STOESSER, M.D., Clinical Professor of Pediatrics and Allergy, School of Medicine, University of Minnesota, Minneapolis, Minnesota

* * *

There will be a 10-minute discussion following each paper

3:30- 4:00 **RECESS TO VISIT EXHIBITS**

4:00- 4:10 **Adeno-Tonsillectomy and its Relation to Asthma**

GERTRUDE SOBEL, M.D., Department of Allergy, Mount Sinai Hospital, New York, New York

4:20- 4:40 **Emotional Aspects of Pediatric Allergy**

JOHANN R. MARX, M.D.,* Department of Psychiatry, Colorado University Medical School, Denver, Colorado

4:50- 5:00 **Allergic Toxemia in Children**

FREDERIC SPEER, M.D., Department of Pediatrics, University of Kansas, Kansas City, Kansas

* * *

There will be a 10-minute discussion following each paper

*By invitation

6:00 **Cocktail Hour—Grand Ball Room**
Courtesy of the Schering Corporation, Bloomfield, New Jersey

7:00 **Banquet—(dress optional)—Grand Ball Room**

WEDNESDAY, APRIL 29, 1953

Morning Session—Grand Ball Room

SECTION ON PSYCHOSOMATIC ALLERGY

Chairman: HAROLD A. ABRAMSON, M.D., New York, New York

9:00- 9:20 **Continuation Report on Psychotherapy in the Asthma-Eczema-Hay Fever Syndrome**

HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York.

9:30- 9:50 **A Common Sense Approach to Psychotherapy in Allergic Practice**

WILLIAM KAUFMAN, Ph.D., M.D., Bridgeport, Connecticut

10:00-10:30 **RECESS TO VISIT EXHIBITS**

10:30-10:50 **Psychotherapeutic Management of the Acute Asthmatic Attack**

HYMAN MILLER, M.D., Beverly Hills, California, Associate Clinical Professor of Medicine, University of California at Los Angeles Medical School, Los Angeles, California

DOROTHY W. BARUCH, PH.D.,* Beverly Hills, California

11:00-11:20 **Personality and the Asthmatic Child**

M. MURRAY PESHKIN, M.D., Consulting Allergist, The Mount Sinai Hospital, New York, New York

* * *

There will be a 10-minute discussion following each paper.

TO BE READ BY TITLE

Urticaria Caused by Bacterial Infections
HERMAN A. HEISE, M.D., Milwaukee, Wisconsin

Clinical Experiences with Co-Pyronil
SALVATORE N. SALETTA, M.D., Chicago, Illinois

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*By invitation

Entertainment

MONDAY, APRIL 27, 1953

12:00-12:45 **TV show—Station WGN**

1:00- 3:00 **Luncheon—Home Arts Guild**

3:00- 5:00 **Tea, coffee and cookies served to members and wives.**
(Courtesy The Chicago Society of Allergy)

TUESDAY, APRIL 28, 1953

12:00 **Luncheon at Henrici's in Merchandise Mart,** followed by tour of Merchandise Mart—$2.50 (including tax and gratuities)

3:00- 5:00 **Tea, coffee and cookies served to members and wives.**
(Courtesy The Chicago Society of Allergy)

6:00- 7:00 **Cocktail Party—Grand Ball Room**
(Courtesy The Schering Corporation)

7:00 **Banquet—Grand Ball Room (dress optional)**
(Wine—Courtesy The Nepera Chemical Company)
(Perfume atomizers for the ladies—Courtesy The DeVilbiss Co.)
(Floor show and orchestra courtesy of those listed below)

Chicago offers many interesting tours. Notices regarding these tours will be posted during the convention.

* * *

We are indeed grateful to the sponsors who have furnished the necessary funds for entertainment and scholarships for the Ninth Annual Congress. A list of these sponsors will appear in the final program.

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RHEUMATIC ACTIVITY IN BACTERIAL ENDOCARDITIS—ANTISTREPTOLYSIN MEASUREMENTS

ANDREW KERR, JR., M.D.
New Orleans, Louisiana

THE MAJORITY of patients who develop bacterial endocarditis have previously had rheumatic fever.[3,28] The most common causative organism of bacterial endocarditis, the alpha hemolytic streptococcus,[15] is frequently cultured from the blood stream, and some consider its occurrence in the blood as a physiological phenomenon.[13] It would seem the occurrence of such a bacteremia in a patient whose endocardium has been damaged by rheumatic fever would be all that is required for development of bacterial endocarditis. If this were so, one would expect the majority of patients who have had rheumatic endocarditis to develop this bacterial complication. In fact, however, approximately only 5 per cent become afflicted with this dreaded disease.[3,31] A factor, or factors, other than the above two must act in the development of bacterial endocarditis in rheumatic subjects.

Such factors could be either (1) a change in the virulence of the organism, or (2) a change in the resistance of the host. There is no evidence to indicate that the ordinarily mild alpha hemolytic streptococcus is changed from its usual characteristics when it becomes the causative organism of bacterial endocarditis.[6,10] The change in reactivity of the host could be either by an alteration of circulating antibodies or a change in fixed tissue response. Almost all studies are in agreement that the host possesses circulating antibodies in abundance against the alpha hemolytic streptococcus causing the bacterial endocarditis.[6,12] We will concern ourselves here with a consideration of the change in the fixed tissues of the host.

The experimental production of a state of hypersensitivity in animals was noted by several German investigators[5,24,29] to alter the cellular structure of the heart's lining. They postulate that this allergic change would permit a bacterial nidus to establish itself on the endocardium. Siegmund,[26] Jaffé,[11] and Allen[1] studied the cellular change in the endocardium in bacterial endocarditis. Siegmund indicated the earliest change was a swelling of the subendothelial connective tissue fibers. Jaffé and Allen demonstrated that these swollen fibers progress to a fibrinoid necrosis involving the mesenchyma. On this necrotic base bacteria were seen to proliferate. Jaffé noted the similarity of this response to that seen in allergy. Siegmund observed this fixed tissue response not only in bacterial

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endocarditis but in other infections as well. In addition, Siegmund noted a similar endothelial proliferation and necrosis of the arterioles in bacterial endocarditis and in other infectious diseases. Marked examples of this arteriolar lesion were demonstrated in bacterial endocarditis by Ottander,[23] Merklen and Wolf,[19] and Lian, Nicolau and Poincloux.[14] These authors called attention to the resemblance of these lesions to those of hypersensitivity.

Grant, Wood and Jones[7] noted that the endothelium beneath the site of bacterial implantation showed a reaction similar to that of acute rheumatic fever. Moore[20] indicated that the initial lesion, or response of the endocardium, was the same in both rheumatic and bacterial endocarditis. Harper[10] preferred to interpret the changes in the valve in terms of its reticuloendothelial function, but noted that recurrent rheumatic fever may adversely affect this function to permit bacteria to localize.

Evidence for the recurrence of acute rheumatic fever preceding the onset of bacterial endocarditis is seen in the studies of Clawson and Bell,[4] Buchbinder and Saphir,[2] Von Glahn and Pappenheimer,[30] and McIllwaine.[18] These pathologists noted Aschoff nodules in a high percentage of the hearts of patients who died from bacterial endocarditis. In several instances the verrucous lesions of acute rheumatic fever were found in the same valve attacked by bacterial endocarditis. These lesions, however, were not interpreted by Gross and Fried[8] to mean active rheumatic fever. In addition, the specificity of the Aschoff nodule has been seriously questioned by the studies of Hall and Anderson.[9] Nevertheless, McIllwaine's recent study is worthy of consideration. In 65 per cent of seventeen cases of bacterial endocarditis, Aschoff nodules were found which corresponded closely in age to the estimated duration of the patient's bacterial infection.

A study of a circulating antibody was undertaken to bring evidence of another nature—that concerning the question of active rheumatic fever initiating the bacterial infection. Since a significant number of patients with acute rheumatic fever exhibit an elevation of antistreptolysin –O– titers in response to the preceding beta hemolytic streptococcal infection,[21,25] this antibody was determined in a group of patients with bacterial endocarditis. Previous reports of such titers in patients with bacterial endocarditis are meager and inconclusive.[17,22]

MATERIAL AND METHODS

Weekly measurements of the antistreptolysin –O– titers were determined in sera from twenty-four patients with bacterial endocarditis.[27] From sixteen of the patients a causative organism was isolated from the blood stream, the bacteria being alpha hemolytic streptococcus in twelve instances and Staphylococcus aureus in four instances. In eighteen of the patients it was believed rheumatic endocarditis had antedated the bacterial infection. In all but seven instances, antibiotic therapy had been started before the titers were drawn.

TABLE I. SERIAL (WEEKLY) ANTISTREPTOLYSIN -O- TITERS IN SUBACUTE BACTERIAL ENDOCARDITIS

	With Rheumatic Heart Disease Median = 1/128								
	1/83 1/83 1/83 1/62.5 1/62.5 1/62.5 1/62.5	1/100 1/159 1/100 1/125 1/125 1/125 1/159 1/159 1/125	1/100 1/125 1/100 1/100 1/59 1/159	1/125 1/125 1/200 1/100 1/100 1/250	1/125 1/159 1/125 1/159 1/125 1/250 1/159	1/200 1/200 1/200 1/200 1/200 1/200 1/200	1/200 1/250 1/400 1/500 1/500 1/400 1/500 1/500 1/500 1/500	1/317 1/250 1/317 1/250 1/317 1/317 1/317 1/317 1/317	1/317 1/317 1/317 1/317 1/317
Organism	None	Alpha Hem. Strep.	Alpha Hem. Strep.	Staph. Aureus	Staph. Aureus	Staph. Aureus	None	Alpha Hem. Strep.	None
	1/50 1/62.5	1/50	1/50	1/83.3	1/83 1/83 1/83	1/100 1/62.5 1/100 1/125	1/125	1/200 1/200	1/250 1/400 1/200
Organism	Alpha Hem. Strep.	Alpha Hem. Strep.	None	Alpha Hem. Strep.	None	None	Alpha Hem. Strep.	Alpha Hem. Strep.	Alpha Hem. Strep.

	With Other Types Of Heart Disease Median = 1/125					
	Congenital Heart Disease		Syphilitic Heart Disease	Previously Normal Heart	? Congenital Heart Disease	? Syphilitic Heart Disease
	1/159 1/250 1/250 1/200 1/250 1/250 1/250	1/250 1/159 1/317 1/317	1/125	1/83 1/100 1/125 1/100 1/125	1/317 1/400 1/400 1/400 1/400	1/50 1/50 1/62.5 1/50 1/50
Organism	None	None	Alpha Hem. Strep.	Staph. Aureus	Alpha Hem. Strep.	Alpha Hem. Strep.

RESULTS

The 110 titers (Table I) are remarkable for their consistency and for their failure to demonstrate any significant difference from normal levels. No difference is evident in titers of patients when grouped according to the underlying type of heart disease, the causative organism, or time or type of therapy.

CONCLUSION

In this study of rheumatic activity in bacterial endocarditis, the titers of antistreptolysin –O– do not indicate recent rheumatic activity.

SUMMARY

Students of subacute bacterial endocarditis agree upon the existence of an initial change in the endocardium permitting bacterial vegetations to localize on the heart's lining. Several observers consider this change to be allergic in nature. Pathologists have presented evidence that acute rheumatic fever instigates this reaction of the endocardium in patients who develop

bacterial endocarditis. A study of the titer of a circulating immune substance, antistreptolysin –O–, which is usually elevated in patients with acute rheumatic fever, was undertaken in patients with bacterial endocarditis. Tests of 110 serial titers of this substance from twenty-four patients with bacterial endocarditis did not demonstrate significant elevations.

ACKNOWLEDGMENT

The author wishes to express his gratitude to Miss Joan Floyd for her technical aid in this study.

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Louisiana State University School of Medicine
Department of Medicine

GERMAN SOCIETY FOR ALLERGY RESEARCH

The Third Assembly of the German Society for Allergy Research will be held at the assembly hall of the University Eye Clinic, Frankfort on the Main, on April 11 and 12, 1953.

Principal topics will be:

1. Allergy and Pathologic Anatomy
2. Allergy Clinic
   (A) Normergic and Hyperergic Inflammation—DR. LETTERER, Tübingen
   Importance of Allergy Instruction in Pathology—DR. VON ALBERTINI, Zürich

   Discussions by Dr. JECKELN of Lübeck, DR. MENKIN of Philadelphia, DR. NORDMANN of Hannover, and DR. SIEGMUND OF Münster, Westf.

   (B) Brief Résumé of the Introductory Topic—DR. KÄMMERER, München.

This will be followed by individual reports.

PROF. DR. W. KIKUTH, *Chairman*
PROF. DR. K. HANSEN, *Secretary*

ALLERGY TO ENDOGENOUS HORMONES

A. FORD WOLF, M.D., F.A.C.A.
Temple, Texas

H. A. BAILEY, M.D.
Dallas, Texas

JOHN M. COLEMAN, M.D.
Chicago, Illinois

THE PURPOSE of this presentation is to call attention to an intriguing and poorly understood phase of allergy. Endogenous endocrine allergy, or the development of sensitivity to one's own hormones, presents some very interesting problems from the clinical as well as allergic and immunologic standpoints.

Endogenous allergy is exemplified by two well-known processes. Sympathetic ophthalmia is an allergic response to a patient's own uveal pigment. It generally results only after damage to the uveal tract. Such damage apparently induces the formation of a uveal pigment allergen, possibly through a hapten linkage. The second classic example of endogenous allergy is paroxysmal hemoglobinuria. Donath and Landsteiner[3] showed the presence of an antigen-antibody reaction with production of autohemolysins which hemolyse the patient's own erythrocytes on exposure to cold.

We are all familiar with premenstrual and menstrual flareups of allergic symptoms in women with asthma, urticaria, and so on. Likewise, we see instances where symptoms occur only in relation to the menstrual cycle.

Geber[4] did some of the very early experimental work on this subject. In a patient having premenstrual urticaria, he demonstrated that if serum obtained premenstrually was injected intravenously during the intermenstruum, urticaria was produced. Premenstrual serum from controls did not produce this response. Hence, he reasoned that there were substances in the blood at the premenstrual time to which that patient was sensitive. In 1935, Geber[5] reported successful desensitization by repeated intracutaneous injection of such serum. Several other investigators confirmed this finding.[6,8,12]

Urbach,[12] in 1939, and Cameron,[2] in 1940, reported relief of symptoms of certain patients with acne and headache treated with premenstrual serum.

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Other syndromes with definite premenstrual association were lessened or abolished by such therapy.

Phillips,[9,10] in 1943 and 1949, reported that some patients with premenstrual headache and premenstrual tension syndromes had immediate wheal type positive skin tests to Synapoidin.® This is a mixture of chorionic gonadotropins and anterior pituitary hormone. He was able to give relief to about 70 per cent of patients by intradermal injections of very small doses of a 1:5 dilution. The amount used seemed much too small to produce any effect by direct hormonal action. The average dosage was only 0.09 cc twice a month.

Other indications of the existence of hormonal allergy include:

1. Demonstration of skin-sensitizing antibodies for hormones.[13] One may use either the crystalline hormone in aqueous solution or a solvent of oil such as olive, sesame, or peanut.
2. Recurrent test reaction. This is a flare-up in a previous test site brought about by injection of the same hormone in a different site at a later date.
3. Retarded periodic reaction. Here, there is reaction at previous test sites at the premenstrual time, possibly because certain hormone levels in the body are at their height.
4. Demonstration of specific antibodies in serum of patients by passive transfer as carried out by Salen[11] and Zondek and Bromberg.[13]
5. Properties of reagins induced by hormone allergens similar to those of allergic reagins in general.[13]
6. Relief from desensitization in a significant number of patients treated.

Zondek and Bromberg[13] reported that skin tests with crystalline hormones in aqueous solution are not reliable. They postulated that because of their relative insolubility the hormonal antigens did not remain in contact with the cells long enough to produce a reaction. An oil vehicle was used and it was found that preheated olive oil produced fewer control reactions than other oils.

Most observers[1] have followed the suggestion of Zondek and Bromberg[13] in skin testing and have used a deep intradermal or shallow subcutaneous injection. Superficial intradermal injections were found to produce false positive reactions.

Heckel[7] noted considerable variation in sensitivity of the skin. Patients whose tests were negative one day might react strongly to several substances on another. He showed that positive skin tests occurred in apparently normal people, and he concluded that skin sensitivity to steroid hormones is non-specific and variable. Most of those who reacted to steroids did so to several of them. Heckel believes that pregnanediol, the excretion product of progesterone, is the chief hormonal allergen. He states it is present only premenstrually when most symptoms occur and that it is more apt to

cause symptoms than a steroid such as estrogen which is probably present all the time. It is biologically inactive and is thus particularly adapted to desensitization treatment. He administers it orally or subcutaneously and reports relief in about 85 per cent of patients with premenstrual tension.

The authors began working with hormonal allergy in a limited fashion at the Scott and White Clinic in 1949. A great deal of difficulty was encountered in interpreting the skin tests. Very often patients showed positive reactions to several or all of the solutions, both aqueous and in oil. There were no systemic reactions from testing and in no instance did it precipitate a severe headache, asthma, urticaria, or other significant symptoms.

Aqueous extracts produced the immediate wheal type of reaction and occasionally a twenty-four hour positive reaction. Oil solutions infrequently produced immediate reaction. Their usual positive reaction was a tuberculin type erythematous wheal which reached its maximum in twenty-four to forty-eight hours. At times, the reaction did not reach its height for four to six days. In a few patients with negative immediate and twenty-four hour readings, positive reactions at the test sites occurred at the next one or two premenstrual times. When such recurrent reactions were encountered at subsequent menstrual periods, it was found that in most instances every area where an oily vehicle was injected flared about equally. The explanation of these recurrent periodic reactions is obscure. The fact that multiple reactions usually occur suggests that such sensitivity is not specific for any single hormone.

In general, no better therapeutic results were obtained by desensitization in the group with delayed periodic reactions than in those without such reactions. Six patients with this type of delayed reaction were treated. Two obtained complete relief, one partial relief, and the other three no relief. Hence, it is not felt that the delayed periodic reaction is an indication of specific sensitivity, nor is desensitization more apt to be of value in this group.

It seems logical to assume, however, that some type of sensitization mechanism occurs in this situation. Simple hormonal imbalance could not produce these delayed periodic skin reactions. As yet, neither their clinical nor immunologic significance has been determined. It is possible that the oil vehicle serves as a hapten which unites with some substance elaborated during certain phases of the menstrual cycle.

The size of the skin test reaction could not be correlated with good or bad results in treatment. Thus, the skin test is of no aid in helping select patients most apt to get relief by desensitization. This work does not point to any new theory to explain these delayed or delayed periodic reactions, and the theories previously advanced seem inadequate to explain the observed facts. Some of the cases of premenstrual tension, headache, pelvic pain, and skin disturbance may be due to hormonal allergy. Undoubtedly,

many such cases are due to hormonal imbalance alone without any allergic component. There are no definite guide posts to separate the allergic from the nonallergic. Symptoms may be almost identical in spite of the difference in etiology. It is unfortunate that no definite dependence can be placed on history, skin tests or other laboratory or clinical findings to determine which are due to hormonal allergy and which are due solely to hormonal imbalance. Patients selected for desensitization were generally those with positive history of other allergy in whom hormonal or other treatment had failed to relieve symptoms. Several patients are being given a thorough trial with other types of treatment and will be offered hormonal desensitization if relief is not obtained otherwise.

Our work can be summarized as follows: Materials used for skin testing were peanut oil control, sesame oil control, estradiol, estrone, percorten, progesteron, pregnanediol (started 1952), testosterone, insulin, and Synapoidin.® From September, 1949, to January, 1952, skin tests were done on 117 women patients. Twenty of these showed 2 plus reactions to one or more hormone solutions in twenty-four hours, and forty-seven patients showed 1 plus reactions. Peanut oil gave seven, and sesame oil gave six, 2 plus reactions in twenty-four hours.

Twenty-six patients were treated by desensitization. Complete relief was obtained by six, while partial relief was secured by four patients. Eleven patients were not helped. We were unable to follow the other five. Solutions used in treatment were Synapoidin,® sixteen patients; estradiol, ten patients; and progesterone, three patients.

CONCLUSION

1. Sensitivity to endogenous hormones may occur.

2. Symptoms such as premenstrual tension, headache, pelvic pain, urticaria and exacerbation of symptoms in certain dermatoses and asthma may be clinical manifestations of endogenous hormone sensitivity.

3. Skin tests may be of some help in detecting hormonal allergy but at the present time they are difficult to interpret and cannot be relied upon.

4. Desensitization with hormonal substances gave some relief to ten of our twenty-six patients treated.

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Scott & White Clinic (Dr. Wolf)

ENZAR

In an attempt to utilize the known fibrinolytic properties of trypsin, The Armour Laboratories have been conducting an intensive investigative program designed to establish the therapeutic value of intravenous use of the enzyme in diseases marked by accumulation of fibrin, both in the form of major intravascular clots and also in small intracapillary and intralymphatic plugs. A highly purified crystalline trypsin was prepared under the name of Enzar, and this is the material which has been used throughout these studies.

Studies soon revealed tremendous species difference in response to the intravenous use of trypsin. Toxicity was measured by the standard LD_{50} procedures. While the LD_{50} studies were under way, trypsin was injected into the heart chambers of rats in doses and concentration far above the expected levels of tolerance without harm to the animals or a deleterious response. It was hoped that techniques might be developed which would make use of the hydrolyzing effect of trypsin on fibrin and fibrinogen without causing series disturbances in other body functions. These studies suggest that trypsin could be used intravenously in mammals if the dose, concentration and rate of infusion were carefully regulated.

Enzar hydrolyzes various proteins which are not incorporated in organized proplasmic units and hence are not protected by high local concentration of trypsin inhibitor. This latter substance is a proteinoid which is found in great abundance in serum and in the membranes of living cells. Trypsin has a great affinity for this substance and combines with it to form a stable, irreversible, stoichiometric compound. Regardless of the total amount of trypsin injected, only from 1 to 3 per cent becomes available as free tryptic activity. The remainder becomes bound with trypsin inhibitor. Not only is the trypsin activity depleted but the trypsin inhibitor (anti-proteinase) activity diminishes as well. This may be of considerable clinical importance in view of findings indicating that trypsin inhibitor levels are increased in a wide variety of conditions, including acute infections such as pneumonia and typhoid fever, chronic diseases such as rheumatic fever and tuberculosis, hyperthyroidism, and various stages of malignancy and anemias. In short, this is a nonspecific response to a wide variety of pathological conditions.

Some workers feel that trypsin causes elaboration of histaminoid substances from various tissues with resultant side reactions. This re-emphasizes the importance of antihistaminizing patients receiving Enzar, because failure to do so might conceivably result in a severe reaction. This reaction should not be confused with an antigen-antibody type of response; there is considerable evidence to indicate that trypsin is an extremely weak antigen, both from the biochemical and immunologic points of view. Clinically, it has been observed that inflammation of all types responds to Enzar therapy, but the cause-effect relationship is not clearly understood.

Satisfactory results have been reported with the use of Enzar in the treatment of acute thrombophlebitis, thrombotic episodes involving the retinal vessels, chronic thrombophlebitis and a few cases of pulmonary infarction. Preliminary studies on its use in the treatment of infectious diseases of all types, particularly chronic disease entities and those refractory to antibiotic therapy, have shown very interesting results. There are also encouraging reports of results of Enzar therapy in thromboangiitis obliterans, necrotic tissue associated with metastatic carcinoma, acute rheumatoid arthritis, and a number of other conditions. Before attempted use of Enzar, however, very careful instructions should be obtained from The Armour Laboratories, 520 North Michigan Avenue, Chicago 11, Illinois.

AN IMPROVED ALLERGY TESTING SYRINGE

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INTRADERMAL testing is an indispensable part of the allergists' armamentarium, as it provides information on the patients' sensitivities that can be obtained in no other way. Unfortunately this technique calls for a generous supply of small syringes, which are expensive to buy and maintain. The syringes most commonly used are the familiar 1 cc tuberculin type, with ground plungers of glass, and the Cooke type with a drawn glass barrel and a metal plunger wound with asbestos string.

All-glass syringes have the major disadvantage that breaking either part renders the other useless and the whole syringe must be replaced at considerable expense. The Cooke type plunger is indestructible and broken barrels are replaced fairly cheaply. However, the asbestos packing has to be replaced frequently as it gets stained, is tedious to wind for a smooth uniform fit, and it presents a large absorbing surface.

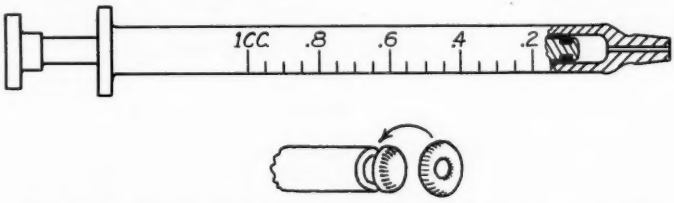

Fig. 1. Cross section and outline drawing of new allergy-testing syringe, showing silicone "O" ring (solid black) resting in notch at end of plunger. Enlarged detail view shows the ring and end of plunger.

A syringe design that is superior to either one of the common types makes use of a drawn glass barrel, a metal plunger and a small silicone "O" ring as the seal. Figure 1 shows the essential features of this syringe.

The silicone ring is an almost ideal device for sealing a fluid pump plunger. The material is plastic enough so that it adapts itself to small irregularities in the barrel diameter. It is self-lubricating, as it slides on the minute film of liquid that adheres to the glass. Silicone is extremely inert, is non-adsorbing, and can stand wide ranges of temperature. Rings that have been boiled and cooled 200 times show no change in characteristics.

Because the ring sits in a groove in the metal plunger, any lateral pressure tends to force the upper part of the ring between the shoulder of the groove and the glass. The greater the pressure that is applied, the tighter the seal. This principle is used successfully in hydraulic pumps in aircraft

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where very high pressures are encountered. If for any reason a ring needs replacing, it is easily rolled out of its groove and a new one slipped in.

In order to test the syringe for adsorption of antigen, which might result in cross contamination, the following experiments were carried out.

Syringes were partially filled with concentrated Endo's house dust extract, 5 per cent glycerinated *Dactylis glomerata* extract, and buffered saline extract of *Lolium perenne* containing 20,000 protein nitrogen units per cc. They were allowed to stand for one hour, then emptied and rinsed ten times with sterile distilled water. One-quarter cc of the last rinse was allowed to stand in the syringe for fifteen minutes, then used for testing on a subject known to give 4 plus reactions to these three antigens. All three gave slight positive (1 plus) reactions. The syringes were then cleaned in the usual fashion and sterilized by boiling. Again 0.25 cc of distilled water was allowed to stand in the syringes for fifteen minutes. Intradermal tests with this fluid were negative.

In a second experiment, the syringes were allowed to stand containing Endo's house dust extract 0.25 per cent, *Dactylis glomerata* glycerinated at 0.5 per cent (1:200) and *Lolium perenne* saline at 2,000 protein nitrogen units. These represent commonly used testing concentrations. After rinsing ten times as before, intradermal tests were essentially negative, and after cleaning and boiling the tests were completely negative.

SUMMARY

An improved type of allergy testing syringe is described. It consists of a drawn glass barrel, a metal plunger and a silicone "O" ring as the seal. The silicone is impervious to sterilizing temperatures and does not adsorb antigen to any appreciable extent. The glass barrels and the silicone rings are readily replaceable.

127 North Madison Avenue

AN EFFECTIVE METHOD FOR THE TREATMENT OF PRURITUS WITH THE ORAL USE OF PROCAINE HYDROCHLORIDE-ASCORBIC ACID COMBINATION

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THE ORAL administration of procaine hydrochloride with ascorbic acid offers an effective method for the treatment of allergic patients complaining of pruritus. Striking results have been obtained in the thirty-one cases studied, symptomatic relief having been reported to continue from four to six hours. Patients were given tablets containing 250 mg of procaine hydrochloride and 150 mg of ascorbic acid.* They experienced almost immediate relief, and with the itching alleviated, cessation of scratching allowed their excoriations to heal without further disturbance. In this series of cases other treatment has been in progress for some time without any such relief; consequently, these served as controls.

Clinically, procaine has been in use for over fifty years as a local anesthetic, and is considered about one-fourth as toxic as cocaine. Procaine is broken down in the plasma and in the liver to para-aminobenzoic acid and diethylamino-ethanol, the end products being excreted by the kidneys. State and Wangensteen[6] in reviewing the pharmacology of procaine state that it affects all living cells, but its main action is the anesthetizing effect on the nerve fibers carrying pain stimuli from the muscles and joints.

Among the first to report on the oral use of procaine were Schapiro and Sadove[5] who noted that a patient with status asthmaticus was unable to receive any appreciable degree of relief until procaine was administered orally.

Roka and Lajtha[4] gave procaine orally to several hundred cases with spastic pylori, and recommended it as a single therapeutic procedure. They found it useful as a preparation for surgical intervention in cases of organic pyloric obstruction, and also used procaine orally to prevent reflex response to local irritation as produced by rubbing with the oliva.

Ellis[1] thought that since procaine is readily absorbed from the gastrointestinal tract, if a sufficient amount could be absorbed without ill effect, a generalized systemic effect could be achieved, as it is when procaine is injected intravenously. He writes of fourteen cases who were given oral procaine to relieve their pain and pruritus. In all he gave over 200 doses, and concluded that oral procaine was effective in the relief of severe pruritus and some types of pain, namely, pylorospasm and arthralgic and

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*Procaine Hydrochloride-Ascorbic Acid tablets supplied through the courtesy of Dr. L. E. Josselyn, Abbott Laboratories Research Division, North Chicago, Illinois.

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myalgic states. He employed dosages ranging from 1 to 3 gm every three to six hours.

Markow, et al[3] in their study on the oral use of procaine in the treatment of bronchial asthma and other allergies, did not feel that it gave satisfactory results in a sufficient percentage of their cases and found a high incidence of side reactions even with the addition of ascorbic acid. Their experimental formula contained 300 mg of procaine hydrochloride and 100 mg of ascorbic acid.

No side effects due to orally administered procaine-ascorbic acid combinations were present in Luddecke's[2] study of ten patients with allergic disorders. Various drugs in combination with procaine were tried. Four patients were given combinations of 250 mg procaine, 10 mg ephedrine and 15 mg methapyrilene several times a day, and one patient was given 300 mg of procaine hydrochloride every three hours. He reports that pruritus was relieved without recurrence in all except one patient.

Luddecke felt that he obtained better results with the use of 250 mg of procaine hydrochloride and 150 mg ascorbic acid. This was tried on five patients who had previously had antihistamines and other drugs without effect. He believed, however, that ascorbic acid does not exert the main therapeutic action, but rather a synergistic action with the procaine.

In the present study the same combination of procaine hydrochloride and ascorbic acid was used, with tablets taken every four hours or as needed.

CASE REPORTS

Case 1.—I. H., a girl, aged sixteen, showed positive tests to dust, Alternaria, Hormodendrum and animal danders. The diagnosis was atopic dermatitis. Itching was reported relieved within fifteen to twenty minutes following the administration of a procaine-ascorbic acid tablet. The lesions started to heal when the scratching was discontinued.

Case 2.—F. S., a woman, aged thirty-one, showed positive tests to dust, molds and animal danders. The clinical diagnosis was urticaria. Itching was relieved and hives cleared up within sixteen hours after medication. The pruritus vulvae was also relieved, and the excoriations cleared.

Case 3.—M. L., a fifty-one-year-old man, had a contact dermatitis due to acetone. Itching was relieved symptomatically a few minutes after administration of tablets.

Case 4.—S. D., an eight-year-old girl, showed positive tests to eggs and apples. The diagnosis was atopic dermatitis. Within ten minutes after taking a tablet, itching was relieved and excoriations cleared.

Case 5.—E. M., a woman aged twenty-eight, had a contact dermatitis of the face due to cosmetics. Itching was relieved a few minutes following ingestion of tablet. Pruritus vulvae was relieved at the same time.

Case 6.—H. R., an eight-year-old girl, showed positive tests to wheat and dust. Her diagnosis was atopic dermatitis. Itching was relieved three to five minutes after taking a tablet and relief continued for eight to ten hours at a time. She also had scabies and obtained relief from this; however, antiscabetic measures were carried out later.

Case 7.—J. R., a girl, aged six, was positive to tests with wheat and dust. Her

diagnosis was atopic dermatitis. Itching was relieved from three to five minutes following medication and relief continued for about six to eight hours. This patient also obtained relief from the pruritus of scabies; antiscabetic measures were carried out later.

Case 8.—W. M., a thirty-year-old man, was positive to tests with dust and fish and his diagnosis was urticaria. Relief came a few minutes following use of the procaine-ascorbic acid tablet, and lasted about five hours. Hives were still present after several weeks, but the itching disappeared after use of tablets. Placebos and other medication had not relieved the pruritus. The pruritus ani was also relieved by the procaine-ascorbic acid tablets.

Case 9.—S. Z., a girl, aged seventeen, was positive to tests with codfish, dust and ragweed. Her diagnosis was atopic dermatitis. Itching was relieved a few minutes following ingestion of the procaine-ascorbic acid tablet. The combination tablet also alleviated the itching locally in the area of injection.

Case 10.—C. Z., a boy, aged thirteen, was positive to tests with dust, ragweed and wheat. Relief from itching occurred a few minutes following medication, and continued for three to four hours.

Case 11.—M. I., a woman aged forty-five, had a contact dermatitis in the area around her external ear due to plastics. Relief from itching occurred within ten minutes following oral ingestion of procaine-ascorbic acid. It also alleviated the pruritus vulvae and ani.

Case 12.—M. L., a forty-six-year-old woman, was positive to tests with dust and Alternaria. Her diagnosis was atopic dermatitis. Relief from itching occurred a few minutes following medication. It also alleviated the pruritus vulvae.

Case 13.—L. H., a woman, aged forty-one, had a contact dermatitis of the ears due to phenol in ear drops. Relief occurred within a few minutes following procaine-ascorbic acid medication and lasted for five to six hours.

Case 14.—J. D., a seven-year-old boy, was positive to tests with dust, wheat, Hormodendrum and milk and had an atopic dermatitis. Itching ceased a few minuates following oral ingestion of procaine-ascorbic acid and relief continued for four to five hours at a time.

Case 15.—P. B., an eleven-year-old girl, was positive to tests with onion, wheat, milk and dust and had an atopic dermatitis. Patient reported relief within a few minutes, which lasted for four to five hours.

Case 16.—B. B., a woman aged fifty-three, had an urticaria due to penicillin. She obtained relief within a few minutes after medication and symptoms cleared in two days. Pruritus vulvae was also alleviated.

Case 17.—M. R., a thirty-year-old woman, had seborrhea of the scalp. She obtained no relief from procaine-ascorbic acid.

Case 18.—M. L., a woman aged sixty-four, had a contact dermatitis to detergents. She obtained symptomatic relief within fifteen minutes, which lasted two to three hours at a time. Pruritus vulvae was also relieved.

Case 19.—A. L., a man aged thirty, had poison ivy due to *Rhus toxicodendron.* Itching was relieved in about fifteen minutes following procaine-ascorbic acid medication and relief lasted about three hours.

Case 20.—C. N., a seventy-year-old woman, had contact dermatitis due to soaps. Relief was obtained a few minutes after medication, and lasted about five or six hours. Pruritus vulvae was also alleviated.

Case 21.—J. A., an eight-month-old girl had an atopic dermatitis due to wheat, eggs and milk. The patient got no apparent relief from procaine-ascorbic acid. One-fourth tablet was given with no side effects noted.

Case 22.—W. A., a woman aged twenty-four, had a contact dermatitis due to soaps.

She got prompt relief from procaine-ascorbic acid medication and excoriations disappeared. Pruritus vulvae was also alleviated.

Case 23.—R. N., a man aged thirty-one, had an atopic dermatitis and showed positive tests to dust. Relief occurred within a few minutes, lasting four to five hours, after taking tablets. Pruritus ani was also alleviated.

Case 24.—A. N., a thirty-year-old woman, was positive to tests with dust, Alternaria and ragweed. She had an atopic dermatitis. Relief occurred within a few minutes following medication and lasted four hours. Pruritus vulvae was also relieved.

Case 25.—J. H., an eight-year-old girl, was positive to tests with dust, Alternaria, wheat and milk. She had an atopic dermatitis. Relief occurred within a few minutes.

Case 26.—C. B., a woman aged twenty-seven, had a contact dermatitis on legs and feet, probably due to shoe dye. She obtained relief within a few minutes, which continued for four to five hours at a time. Pruritus vulvae was also relieved.

Case 27.—S. Z., a woman aged thirty-six, had poison ivy due to *Rhus toxicodendron.* She obtained prompt relief from tablets; other measures were taken at the same time, however.

Case 28.—C. E., a woman aged thirty-four, had poison ivy. Relief from itching occurred within a few minutes after ingestion of tablets. Pruritus vulvae was also relieved.

Case 29.—C. S., a man aged forty-four, had a contact dermatitis due to soaps, involving the arms and hands. This patient obtained prompt relief after taking tablets; relief continued for four to five hours.

Case 30.—A. L., a forty-two-year-old man, had poison ivy due to *Rhus toxicodendron.* He experienced relief within a few minutes after taking the medication, which lasted for four to five hours.

Case 31.—L. Z., a man aged thirty-four, had poison ivy due to *Rhus toxicodendron.* This patient reported no relief.

DISCUSSION

Procaine hydrochloride with ascorbic acid was tried orally to determine its value in the treatment of allergic patients who complained of pruritus of any nature. There was no effort made to evaluate its effect in other conditions. No placebos were used in this series of thirty-one cases, because these patients had all taken antihistamines and other drugs previous to this study, with no benefit, suggesting that these other medications might be considered as controls.

The results herein reported were highly satisfactory, and, in some cases, dramatic, even though they were of a symptomatic nature. The important factor noted was that the patients felt relieved and did not scratch, thus giving the excoriations, et cetera, an opportunity to heal without further disturbance. The effect on urticaria should be studied further as there were only three cases available at the time. These might possibly have improved anyway, but gratifying improvement did occur with the use of these tablets. One patient still has urticaria off and on, but complains very little of itching after taking the oral procaine.

The application of any new drug in allergic conditions is apt to produce many misleading results, since the conditions governing these results are

TABLE I. RESPONSE TO PROCAINE ASCORBIC ACID

Number of patients*	Condition for which treated	Relief reported	No relief
13	Atopic dermatitis	12	1
3	Urticaria	3	
9	Contact dermatitis	8	1 (partial)
4	Poison ivy	3	1
1	Seborrhea		1
12	Pruritus vulvae	12	
3	Pruritus ani	3	
2	Scabies	2	

Note: One tablet of procaine hydrochloride with ascorbic acid was taken every four hours, or as needed.
*Some of these conditions were concomitant. Thirty-one patients in all were studied.

subject to modifying factors beyond one's control. For example, it was necessary to rely on the subjective reports of the patients. Objectively, the relief accompanied by the healing of the excoriations could also have been coincidentally the result of other treatments which were being continued. However, one must assume that the present medication was in some measure responsible, since treatment had been in progress for some time without relief.

There were no side actions of any note, nor did any of the patients mention reactions. This does not agree with the report of Markow, et al[3] who found that there was a high incidence of headache, dizziness, diarrhea, nausea and itching of the skin. It is possible that these reactions were avoided in this study, because instead of tablets containing 300 mg of procaine hydrochloride and 100 mg of ascorbic acid, tablets containing 250 mg of procaine hydrochloride and 150 mg of ascorbic acid were employed. It is noted that they mentioned only one case of pruritus as a side reaction in these allergic conditions. This is consistent with the findings of the present series. The writer would agree that the procaine-ascorbic acid combination is of no value in the treatment of bronchial asthma or the other allergic conditions such as hay fever, vasomotor rhinitis, et cetera, as these conditions were concomitantly present with pruritus in this study.

No attempt was made to determine the cause of the pruritus vulvae, other than to note that these patients showed cervical erosions, had leukorrhea, or had borne children and showed some form of perineal injury.

It could be noted that none of these cases had diabetes mellitus.

SUMMARY

The results of this study tend to confirm previous impressions that the use of oral procaine with ascorbic acid offers a new and effective method for the treatment of pruritus.

Tablets containing 250 mg of procaine hydrochloride and 150 mg of ascorbic acid were given every four hours, or as needed, to a series of thirty-one patients who complained of pruritus from whatever cause.

Results were highly satisfactory, with dramatic relief reported within minutes. Relief in most cases continued from four to six hours. Up to the present time there does not seem to be any toxic effect due to over-

dosage. There were no side actions of any note, nor were there any reactions mentioned by the patients.

Twelve out of thirteen cases of atopic dermatitis were quickly relieved, while eight out of nine cases of contact dermatitis reported relief, with partial relief in the other. Four cases of dermatitis venenata due to *Rhus toxicodendron* showed three experiencing relief, with one receiving no results. Three cases of urticaria obtained prompt relief. Twelve patients complaining of pruritus vulvae were helped, as well as three with pruritus ani. In two cases of youngsters who coincidentally had scabies, relief was reported before the other antiscabetic measures could be initiated. The results did not seem to be governed by any particular condition, although one case of seborrhea was not benefited.

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Whitman, Massachusetts

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The Texas Medical Center, in the space of seven years, has become one of the outstanding institutions of its kind. It continues to expand with new buildings, new facilities for research, and new teaching programs.

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EXACERBATION OF IVY DERMATITIS BY RHUS ANTIGEN INJECTIONS

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THE HISTORY of the treatment of acute ivy dermatitis is not one of which the medical profession can be proud. As with the "common" cold and the "common" wart the various treatments for ivy poisoning run from forms of black magic through old wives' tales, home remedies, patent medicines, pseudoscientific procedures, and simple palliative measures. As physicians, our fundamental guiding rule should be at least to do no harm to the patient, and I feel that there is in particular one potentially dangerous form of therapy for acute ivy dermatitis that should be carefully avoided.

Thirty years ago several papers appeared praising the use of rhus antigen by injection in treating acute ivy poisoning. Strickler,[10] 1921, Bivings,[2] 1924, Schamburg,[6] 1925, and Alderson,[1] 1925, all reported good results in acute phases of the dermatitis by antigen injection. However, reports gradually appeared which showed a lack of benefit or even harm from the use of the injected antigen during the attack, and work was directed at trying to prove statistically whether or not improvement was found or whether sensitivity could be lessened by such injections.

Coca,[3] in 1922, showed that the incidence of sensitivity to ivy normally increases from childhood to adulthood, reaching a peak of about 90 per cent in adults. Spain and Cooke,[8] 1927, reported no change in the sensitivity to patch tests to ivy even after prolonged injections of an alcohol extract of the rhus toxin. Greenberg and Mallozzi,[4] in 1940, could find no improvement in skin sensitivity after such injections. Several of the cases reported by Spain and Cooke showed flaring of dermatitis in sites of old ivy poisoning with large parenteral doses even though there was no reaction at the site of inoculation. McNair,[5] in 1921, found no improvement in the healing time in seventy-six patients treated by injections, and Sompayrae,[7] in 1938, reported no change in the length of time of healing of ivy dermatitis by his parenteral injections. These varied reports and others led to extreme confusion in the field of rhus antigen injections, and finally in 1945, Stevens[9] published a long, thorough investigation of results to date, along with standards for the preparation of antigen for prophylactic therapy. His conclusions were that since no satisfactory evidence yet shows the course of ivy dermatitis to be improved by such injections, since many patients have been shown to be made worse by such treatment, and since the practice is not in accord with immunological principles,

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the use of the rhus antigen in the treatments of the acute phase of the disease "should be vigorously discouraged." The concluding report of the AMA Council on Pharmacy and Chemistry was "no claim should be allowed for the treatment of the acute dermatitis."

However, in spite of this vigorous protest, the extracts are still being presented to the practitioners in glowing advertisements in our journals, the literature enclosed with the products still carries only the early favorable reports, and the detail men are still recommending their use in the treatment of the acute phase of the poisoning. As the report by Stevens carried no specific cases "made worse by the injections," perhaps a review of four cases from the recent records of the Sharon General Hospital Department of Allergy and Dermatology will be of some value to the general practitioner still faced with the problem of treating acute ivy dermatitis.

Case 1.—A fourteen-year-old schoolgirl with no familial or personal history of atopy had had numerous mild attacks of ivy poisoning every summer for several years. These were always just a few scattered vesicles on the legs or arms and were never severe enough to confine her. Rhus antigen injections had never been administered. About ten days before admission she developed vesicles over both feet and ankles, seemingly an ordinary attack of ivy dermatitis. Her mother heard that one of the physicians "gave shots for ivy," and took the patient there for the injections on the third day of the illness hoping to cure the attack more quickly than usual. Four injections were given daily, more vesicles appearing in the involved areas, and new vesicles appearing higher on the legs, back, abdomen, arms, and face. Two days before admission the blisters on the legs became purulent, red, and swollen, and the patient became feverish.

On admission the patient was found to be in moderate distress with a fever of 101° F, and complaining of pain in both feet and ankles and itching over the entire body. Both feet and ankles were swollen, covered with numerous unruptured vesicles and several large, ruptured, purulent blebs. There were numerous scattered vesicles over thighs, back, abdomen, arms, and face. There was moderate bilateral, inguinal lymphadenopathy. Blood counts showed an elevated white count with a polymorphonuclear leukocytosis. The urine was normal.

She was given penicillin to control the secondary infection and cortisone by mouth, along with mild sedation. Locally, only potassium permanganate washes were given, but all purulent vesicles were opened and cleaned. On the second hospital day a mild papular eruption appeared in the flexures of the forearms, axillae, and neck with a pompholyx-type of eruption on palms of hands. Both of these manifestations disappeared by the fifth day. The patient was discharged on the fifteenth day with all vesicles dry and clean, and suffered no further recurrences.

Case 2.—A thirty-year-old housewife in good general health developed a mild vesicular dermatitis over both forearms about three weeks before admission. She had had numerous previous attacks of ivy poisoning, and this seemed no more severe than the others. She had never had "ivy shots" before. About ten days before admission she received three injections of rhus antigen intramuscularly on alternate days. At the end of this treatment period the dermatitis, which had not been too troublesome before, had now spread rather rapidly over both arms, face, neck, chest, and back and was extremely itchy. On the right forearm where the original vesicles first appeared, a swollen, crusted, oozing area that was hot, tender, and painful developed on the third day before hospitalization.

On examination the patient presented an appearance of moderate distress. Fever was 100° F. Over the entire surface of the arms, neck, face, chest, and back was a confluent, papulovesicular, erythematous eruption with areas of oozing and crusting on neck and both forearms, the right forearm being quite swollen and tender. Blood counts, serology, and urine were normal.

Therapy was started with potassium permanganate washes, and penicillin was given to control secondary infection. Calcium gluconate was used intravenously, and an antihistamine orally for sedative effect. A gradual drying of all lesions was noted, the temperature returned to normal, and on the fourth hospital day all areas were scaling. On this fourth day and again on the tenth day there were mild recurrences of itching, erythema, and fine papulation on both arms, but no further vesiculation or oozing were seen. The patient was sent home with just permanganate washes and antihistamine after the last flare and made an uneventful, complete recovery.

Case 3.—A thirty-four-year-old housewife from a nearby farm had had several mild attacks of ivy poisoning over a period of ten years. There was no family history of atopy. Four weeks before admission typical vesicles appeared on the left forearm after exposure to weeds. The area of dermatitis spread slowly over most of the left forearm with a few vesicles appearing on the right arm about two weeks before admission. Beginning ten days before admission, she received four daily intramuscular injections of an oily rhus antigen with no improvement in the condition of the skin. Only calamine lotion had been used locally. Five days before she was seen an erythematous, maculopapular eruption appeared in the flexures of both arms, spreading rapidly over the entire body by the third day and becoming extremely pruritic.

On the day of admission the patient showed the entire body covered with a confluent, erythematous, maculopapular eruption, most marked in the flexual areas. There were deep, intra-epithelial blebs on palms and soles. Both forearms were crusted and fissured with obvious secondary infection in the deeper fissures. Temperature was 100° F. orally. She was restless and irritable and complained bitterly of constant itching over the entire body. All laboratory work was within normal limits: a mild leukopenia of 4,100 with 48 per cent lymphocytes, blood sugar at 92, normal urine, and negative serology.

The patient was placed on cortisone therapy, penicillin was given in adequate dosage, sedation and antihistamines were used orally to relieve the itching and restlessness, and Burow's solution was applied locally. The temperature returned to normal on the second hospital day, the itching rapidly subsided, the maculopapular eruption faded with mild exfoliation by the seventh hospital day, leaving only a healing, dry dermatitis on the left forearm. This resolved without recurrence after discharge with complete withdrawal of cortisone on the tenth day.

Case 4.—A generally healthy fifty-year-old housewife, brought up in the city, had never to her knowledge had ivy poisoning until the family moved to a new home on the edge of town. There was no familial history of atopy. About two months before she was seen she developed vesicles on one wrist; these dried and healed quite readily. About three weeks before admission she again noted vesicles on both wrists, forearms, and neck, which this time gradually spread over surrounding areas. Two weeks before she was seen she received one intramuscular rhus antigen injection daily for eight consecutive days with a steady gradual spread of the rash. Two days before admission she very suddenly developed a scaling, erythematous, pruritic eruption over the entire body, again most marked on the wrists, forearms, neck, and flexural areas.

On admission the patient was extremely irritable, quite flushed, and presented a

generalized, dry, scaling, erythematous, exfoliating eruption over all areas, most marked in the flexures. Temperature was normal. Blood sugar, serology, blood counts, and urine were within normal limits. Remainder of the physical examination was not abnormal, and no vesicular eruption or pompholyx was found.

The patient was placed on cortisone orally, sedation, washes of permanganate and zinc oil locally. In the following two weeks of hospitalization the eruption faded and scaled and then flared over again with generalized erythema and papule formation with intense pruritis in three cycles, each less intense. She was discharged on the seventeenth hospital day to continue local care only at home. No further recrudescences were noted.

DISCUSSION

The four cases recorded seem to be rather straightforward. In none did the problem of atopy present itself either in personal or family history. In none had there been previous complicating skin disorders. In none had there been local mismanagement that might have produced eczematous, contact dermatitis from too vigorous therapy. All four apparently began as simple ivy dermatitis and grew steadily worse with each injection of the rhus antigen, or else additional sensitivity appeared either in the form of exfoliative dermatitis or pompholyx or both.

The repeated cyclic flaring of the papular, erythematous phase of the dermatitis in cases three and four may be considered merely the escape of the dermatitis from the control of the body's immune system and therapy used. However, as the rhus antigen is in an oily, slowly-absorbed base, injected deeply into the muscles, it is more likely that recurring quantities of the oil are absorbed by the body and produce a flaring of the dermatitis in the sensitized areas.

The injection of such antigen during the acute phase of ivy poisoning does seem contrary to general allergic principles. The patient already presents a system at least temporarily overwhelmed by rhus toxin. How should we expect to induce improvement by then adding a further large dose of such toxin? This treatment seems especially questionable when the patient has not even been previously immunized by the administration of small doses of the antigen within the limits of his tolerance.

It is difficult to explain the occasional "good results" seen by some practitioners injecting the extract during the acute phase of the dermatitis. There would seem to be three possible explanations. The first is the case in which the amount of actual ivy poison is so small as not to arouse the full immune response of the body. Here the injection may well bring about a more complete antibody response and conceivably a more rapid regression of the lesions. The second is the case in which for some reason the immune system is refractory and needs the further stimulus of the sudden huge injection of antigen. In this case as well as in the first it has never been shown, however, that any foreign protein might not act as well in stimulating immune responses. A third possible explanation for the occasional improvement seen is that some few individuals receive by chance just the correct amount of antigen to stimulate

some response. As with other allergy sufferers some patients will tolerate large doses of house-dust antigen or ragweed antigen without a constitutional reaction. Perhaps here, too, a few patients will tolerate and possibly even benefit by the huge dose of rhus antigen. However, until we have some method of determining this level of tolerance, we should not assume that one standard dose will benefit all cases.

SUMMARY AND CONCLUSIONS

Four cases of exfoliative dermatitis following rhus antigen injection are presented from the files of the Sharon General Hospital. It is hoped that as more specific instances of these and other complications of this rather illogical form of poison ivy treatment are brought before the practitioners, this present type of antigen injection will be stopped and more beneficial methods developed.

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HAZARDOUS, INFECTIOUS DISEASES STUDIED AT VIRUS RESEARCH LABORATORY

Highly hazardous and infectious diseases are being studied at close range in a new virus research laboratory just completed at Parke, Davis & Co., Detroit, Michigan.

Under the supervision of Dr. F. D. Stimpert, director of microbiological research, scientists are conducting important experiments involving polio, "Q" fever, the common cold, mumps, measles and other highly infectious diseases, which are difficult in ordinary laboratories.

The new laboratory, a specially designed, self-contained unit, will be equipped for research on viral diseases, including such unusual and hazardous diseases as Japanese "B" encephalitis, equine encephalomyelitis, and Russian Spring and Summer Disease (a tick-borne brain fever).

A SMALL DOSAGE, INJECTABLE ANTIHISTAMINE (CHLOR-TRIMETON MALEATE INJECTABLE) IN THE TREATMENT OF ALLERGIC DISEASES

A Clinical Study

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SINCE 1933 when Forneau and Bovet[7] observed that certain phenolic ethers counteracted histamine action *in vitro* and *in vivo*, there has been a constant and intensive chemical and pharmacologic study of the antihistamines under various experimental and clinical conditions. The phenolic ethers achieved no therapeutic success because of their marked toxicity. However, an intensive investigation of a number of antihistamine compounds by Halpern[8] led to one, 2339 R.P. (dimethylaminoethyl benzylanaline), which was reported in 1942 as less toxic in animals than those previously studied. It was used clinically in France under the name Antergan. Since 1942, because of the marked clinical use of these agents, emphasis has been placed upon the search for antihistamines of increased potency, les toxicity, reduced side effects, longer duration of action and, more recently, those of smaller dosages. These are the criteria which continue to stimulate the investigations of the researchers in this field.

The increasing number of drugs used in pediatrics, geriatrics and the special fields of medicine and surgery, each with its sensitizing potential, will surely increase the number of acute and chronic allergic manifestations unless adequate prophylactic and improved drug allergy methods are instituted.

There are numerous published reports, experimental and clinical, on the pharmacologic activity and therapeutic benefits of the antihistamines.[2,3,4,5,6,11,13] They have proved variously effective in the symptomatic relief of seasonal and perennial allergic rhinitis, urticaria, angioneurotic edema, seasonal or pollen asthma, and to a much smaller degree, atopic dermatitis.

These reports have dealt mainly with the use of tablets, elixirs, syrups and relatively large quantities of aqueous solutions. We have had similar results with the use of antihistamines in these forms but have often wished for and eagerly awaited the arrival of a concentrated small-volume injectable form.

All too seldom do we find a therapeutic agent which is efficient when given in small quantities for the symptomatic control of allergic conditions, yet is economical, stable and relatively non-toxic. Because of the need for a drug with these favorable qualities we became interested in

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the clinical study of Chlor-Trimeton Maleate injectable 100 mg per cc.*

Prior to this study we had used the 0.2 per cent solution (2 mg per cc) with good results in many allergic diseases similar to those reported by others,[1,12] but frequently adequate amounts (1 to 2 cc) of the solution necessary for symptomatic relief produced discomfort and lessened the cooperation of the patient.

In the prophylactic and hyposensitization treatment of allergic conditions we have found the subcutaneous and intracutaneous (if the volume is small enough) injections to be efficacious and the routes of choice. These routes make mandatory the use of small quantities of materials if there is to be a minimum of discomfort. In previous years we found it difficult to hyposensitize many individuals with potent allergens because adequate amounts could not be given for the production of an immune response without eliciting severe local and occasional systemic reactions.

CHLOR-TRIMETON MALEATE INJECTABLE

Chlor-Trimeton Maleate Injectable was supplied to us in 1 cc ampules and 2 cc multiple dose vials of aqueous 10 per cent solution. Each cc contained 100 mg of the drug. Reports of the administration of Chlor-Trimeton to laboratory animals 2 mg per kg of body weight over a period of months produced no abnormalities in the vital organs of the rat and dog. The cellular elements and hemoglobin content of the blood were not altered.[13] This drug has proved to be an effective antihistamine of low toxicity when given by mouth.[5] Chlor-Trimeton has been placed in the class of potent but moderately sedative Antihistamines.[6]

METHOD OF STUDY

The Chlor-Trimeton solution (0.05 cc) or 5 mg was withdrawn from the vial or ampule into a tuberculin syringe, and the quantity of allergen in solution was withdrawn from its vial into the same syringe. The two solutions were rotated and mixed using the method suggested by Sanger et al.[10] The mixture was administered subcutaneously. When multiple allergens are given, each one is mixed with 0.05 cc of Chlor-Trimeton Maleate and the combined medication is injected into different sites.

If a moderately severe local reaction to the combined medication occurred, we increased the antihistaminic solution to 0.1 cc or 10 mg on subsequent administrations. We did not find it necessary to increase the Chlor-Trimeton solution beyond 0.1 cc even if two or three allergens were mixed in the same syringe. However, in mixing various allergens in the same syringe, it is difficult to determine which one is responsible for the untoward reaction.

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*Chlor-Trimeton Maleate Injectable-1-(P-chlorophenyl)-1 (2-pyridyl)-3-N, N-dimethylpropylamine maleate was generously supplied through the courtesy of Dr. George Babcock, Jr., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

In cases of drug allergy with skin manifestations 0.1 cc to 0.2 cc of Clor-Trimeton was injected, depending upon the severity of the clinical manifestations. In weeping dermatoses 0.05 cc (5 mg) in 10 cc physiological saline was given intravenously for a more rapid diminution of the oozing.

When there were severe local reactions with large nodule formations, 0.2 cc of the antihistamine solution was injected directly into the local nodular area.

The concentration of 100 mg rendered the use of the tuberculin syringe most efficacious as the syringe is calibrated in 1:100 cc so that 0.05 or 0.1 cc, or multiples thereof, could be easily measured and read prior to the injections.

Some patients complained of a slight stinging effect after the Chlor-Trimeton injection. However, all of them stated that the biting and burning effects, particularly of glycerinated extracts, were greatly reduced with a combined mixture. The antihistamine probably exerted a beneficial local anesthetic effect.

Our clinical study dealt with the use of Chlor-Trimeton Maleate injectable in 0.05, 0.1 and 0.2 cc administered subcutaneously and intramuscularly and 0.05 cc given intravenously in a few instances to be discussed later. These clinical trials extended over a period of four months.

The group consisted of 226 patients, varying in age from three to eighty-one years, divided into the following categories: allergic rhinitis (seasonal and perennial), urticaria, bronchial asthma (seasonal and perennial), atopic dermatitis with weeping eczema, poison ivy dermatitis, and those receiving injections of aqueous suspensions of procaine penicillin for bacterial infections.

The cases of allergic rhinitis consisted of those patients proved sensitive to grasses, ragweed, house dust and molds, by history, skin tests and specific exposures to suspected allergens.

These patients had received some, but not complete, relief of their symptoms on specific hyposensitization procedures, with a persistence of pruritus of the nose, eyes and throat, lacrimation, rhinorrhea, nasal blockage and cough. The persistence of symptoms may be attributed to their inability to accept adequate dosages of specific extracts without marked local reactions and a few systemic reactions.

Our initial injections consisted of a mixture of 0.05 cc of the antihistamine and the specific extract given subcutaneously in the lateral aspect of the upper arm, alternating the arms on subsequent visits. Each patient was requested to report all untoward reactions on the next visit. If a local reaction ensued we increased the dosage by 0.05 cc, never exceeding 0.2 cc. No local reactions of any consequence were observed after reaching the 0.2 cc level.

All cases selected were those who in previous years had incomplete relief of symptoms and/or had experienced moderate to severe local re-

actions and occasional systemic reactions following the injections of specific allergens. Blood counts (total and differential), hemoglobin concentrations, blood pressures and urinalyses were recorded at the beginning, at four week intervals and at the end of the clinical trials.

The degree of symptomatic improvement was considered marked if it was 80 per cent or more, moderate if 60 to 80 per cent, mild if 50 to 60 per cent and negligible or no improvement if less than 50 per cent.

RESULTS AND DISCUSSION

Allergic Rhinitis.—There were seventy-eight patients of allergic rhinitis studied. Twenty-one of these were sensitive to house dust and tree pollens, eighteen to molds, house dust and grass pollens, and thirty-nine to ragweed pollen alone. There was marked improvement in sixty-two, moderate improvement in twelve and no significant improvement in four. Each of these patients received 0.05 cc of Chlor-Trimeton Maleate Injectable with the specific allergen. Four of the twelve with moderate improvement experienced marked improvement when the dosage was increased to 0.1 cc and two of the four with no improvement received moderate benefit for short intervals (eight to twelve hrs.) with an increase in dosage to 0.2 cc. There was no further improvement on additional increments.

The dosage of the specific allergens in the hyposensititization program could be increased on an average of five to tenfold with the addition of the Chlor-Trimeton Maleate solution.

It is of interest to note that one patient had complained of an allergic purpura of the legs during the height of the ragweed season for four successive years, and another in the group complained of severe dysmenorrhea during the ragweed season for five years. Both of these patients tolerated larger dosages of the ragweed extract with the combined ragweed-Chlor-Trimeton mixture during the past season and exhibited no untoward purpuric reactions or dysmenorrheic symptoms during the period of therapy.

The side reactions of drowsiness and dryness of mouth appeared in four cases receiving the 0.2 cc injections. No reactions occurred with the 0.05 cc injections.

It appears that the antihistamine permits a larger dosage of specific antigens to be introduced into the body for the stimulation of the production of a larger number of protective antibodies,[12] blocks the action of histamine on cell surfaces and reduces the capillary permeability produced by histamine-like substances.

Urticaria.—This group consisted of sixteen cases. Four cases were due to foods (tomato, chocolate, walnut and fish), two cases of generalized urticaria resulted from an allergic response to blood transfusions, and ten cases of acute urticarial response resulted from injections of penicillin.

All of the food-sensitive patients were moderately relieved in twelve

to twenty-four hours by the injection of 0.1 cc of the Chlor-Trimeton Maleate solution twice a day. However, the food-sensitive patients were markedly improved by the ingestion of a Chlor-Trimeton tablet (4 mg) in the morning and at bedtime in conjunction with the injection of the anti-histamine solution. It is possible that the gastrointestinal tract, acting as an accessory portal of entry, facilitates a closer association of the antihistamine with the urticaria-producing food allergen in the general circulation and blocks or inactivates the histamine-like substance at the point of release from tissue cells. These two portals of antihistamine entry (skin and gastrointestinal tract) may provide a required larger amount of blood-borne antihistamine to inactivate previously released histamine-like substance. Maietta[9] has suggested such a mechanism in the therapy of pollinosis.

The ten patients with penicillin-sensitivity exhibited generalized urticaria with areas of papulovesicular eruptions and subsequent weeping of the lesions. Three of these patients had an associated severe angioneurotic edema of the lips, eyelids and scrotum. The dosage of Chlor-Trimeton Maleate used in these cases was 0.1 cc (10 mg daily. The patients with angioneurotic edema, generalized urticaria and severe pruritus received 0.1 cc twice daily. Colloidal oat starch (Aveeno) applications were used also in the latter cases. Moderate symptomatic improvement, chiefly as a result of relief of itching, was experienced within three to six hours with marked subjective and objective improvement within twelve to thirty-six hours.

Recently we have observed a more rapid and marked improvement in weeping lesions following the intravenous administration of Chlor-Trimeton Maleate 0.05 cc in 10 cc of physiological saline.

The two patients with urticaria and marked "tightness of chest" with wheezing immediately at the start of the transfusions with blood, which was compatible on typing, cross matching and as to Rh factor, were treated with 0.05 cc of the antihistamine solution in 100 cc of physiological saline solution. This mixture was allowed to flow at 30 drops per minute into the rubber and plastic tubing conveying the blood, without any untoward reaction on subsequent administrations.

Bronchial Asthma.—Six patients of seasonal bronchial asthma of the ragweed pollen type and five patients of perennial or non-seasonal type were treated with the combined allergen-antihistamine mixture. All of the ragweed pollen or seasonal type were moderately benefited by the 0.1 cc injection. In fact, three children in the group were markedly benefited. This improvement is apparently due to lessening of rhinorrhea and post nasal drip, and an anti-edema effect on the nasal and bronchial mucosa. There was a reduction in the paroxysms of cough in all cases.

Patients with perennial asthma had only insignificant to mild improvement. There was a moderate lessening of cough in four patients on increasing the dosage to 0.2 cc, but the wheezing, tightness of chest and

tenacious sputum remained unaffected. We attempted to increase symptomatic improvement in this difficult group by increasing the dosage to 0.3 cc but a dryness of mouth and drowsiness, followed by jitteriness and an increased tightness of chest and wheezing, ensued. A similar circumstance was the result of clinical trials with an oral antihistamine previously. We must admit, however, that there was a pronounced element of nasal and bronchial infection associated with the asthma in these perennial cases.

Atopic Dermatitis.—There were five patients with atopic dermatitis. Three of these exhibited marked sensitivity to house dust and two showed marked sensitivity to chicken feathers on exposure to these allergens. The extracts of these materials were mixed with Chlor-Trimeton Maleate (0.1 cc) and injected subcutaneously at six day intervals for ten weeks with moderate improvement in the erythematous skin lesions in three, but no improvement in the skin lesions of the remaining two patients. There was marked relief of the pruritus in all of them for twelve to twenty-four hours following the injections. When the antihistamine dosage was increased to 0.2 cc, after two weeks there was slight improvement in the skin lesions of the two formerly unimproved patients. Further increases in dosage to 0.3 cc in these evoked a "jittery" feeling and dryness of the mouth. The daily subcutaneous injection of 0.05 cc prevented pruritic symptoms in four patients.

Two of the above patients exhibited weeping eczematoid lesions with marked improvement of the lesions on two successive injections of 0.05 cc (5 mg) administered intravenously at daily intervals. The lesions recurred six days after discontinuance of therapy. These recurrences were controlled by a return to the antihistaminic therapy by the intravenous route.

Poison Ivy Dermatitis.—Five patients with poison ivy dermatitis were given 0.1 cc of the antihistamine subcutaneously for three successive days with marked reduction in weeping beginning at the end of the first day. Progressive improvement of the inflammatory process and relief of pruritus and stinging sensations began within three to six hours after the institution of therapy. After the first day an antihistamine protective cream (Chlor-Trimeton) was used conjointly as a topical application.

Here again the results were more striking and dramatic when the Chlor-Trimeton Maleate (0.05 cc) was administered by the intravenous route. In two of these patients we gave 0.1 cc of the antihistamine in 100 cc of physiological saline intravenously at 30 drops per minute with excellent and almost immediate relief of pruritus and weeping.

Prophylaxis of Penicillin Allergic Reactions.—We realize that the reactions to penicillin are variable according to various authors and the incidence varies from 2 to 15 per cent. However, if we assume that the

average is 3 to 5 per cent it certainly suggests that prophylactic therapy is indicated.

In a group of 111 patients receiving injections of aqueous Procaine penicillin G 300,000 units to 600,000 units per cc, we mixed 0.1 cc of the Chlor-Trimeton Maleate Injectable with 1 cc of the penicillin in the same (2 cc) syringe after the penicillin was aspirated from a multiple dose vial. The material used was from four different sources of supply. We did not attempt to determine in this study which brand of penicillin was the more allergenic.

These patients received a total of 590 injections (360 of 300,000 units and 230 of 600,000 units). Each patient had received one or more injections of penicillin at some date prior to our study. All patients stated that the combined injections produced less prolonged pain at the site of injection and in no case has there occurred an urticarial eczematous, angioedematous, "serum-sickness-like" illness or variants of the above lesions. The injections were given over a period of four months.

We admit that the series is small and further study of a larger number of cases over a longer period of time might reveal a few allergic reactions, but it appears safe to assume that the allergic response to the mixture would be much lower than that to the penicillin alone.

Side effects were infrequent, consisting of mild drowsiness, jitteriness and dryness of mouth in four patients in this group, with dosages in excess of 0.2 cc (10 mg). There were no significant alterations of blood pressures, urine constituents or hemograms during the period of this clinical study.

SUMMARY AND CONCLUSIONS

1. This clinical study dealt with the use of Chlor-Trimeton Maleate Injectable (100 mg per cc in 226 patients) to determine its prophylactic value and therapeutic effect in allergic states.

2. The use of this solution permits the subcutaneous and intravenous administration of a low dosage, small volume, effective antihistaminic agent without discomfort to the patient.

3. Chlor-Trimeton Maleate Injectable proved to be a valuable therapeutic adjunct in the symptomatic treatment of the urticaria, angioneurotic edema, allergic rhinitis, poison ivy and food allergy in this series. The drug is much less effective in atopic dermatitis and bronchial asthma.

4. This antihistamine solution was highly effective in the prophylaxis of penicillin allergic reactions in our series.

5. The intravenous use of the drug quickly relieved weeping eczematoid eruptions and severe, acute urticarias.

6. In hyposensitization therapy, Chlor-Trimeton Maleate 100 mg per cc combined with an extract of the specific antigen permits the administration of a much larger dosage of the extract in sensitive individuals.

7. The side effects from the use of this drug were low, consisting mainly of slight drowsiness, jitteriness, and dryness of mouth in 4 per cent of

the cases in this series. These side reactions disappeared on discontinuance of the drug.

8. No sensitivity to Chlor-Trimeton Maleate 100 mg per cc developed in our series.

9. There should be no abandonment of the intensive search for the etiologic agent in allergic diseases and specific measures should be instituted for a definitive hyposensitization program. The Chlor-Trimeton-Allergen combination made possible a more adequately functioning hyposensitization program for those individuals who formerly exhibited severe allergic reactions on minimal exposure tc the offending agent.

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6 East Garfield Blvd.

INTERIM MEETING OF THE BOARD OF REGENTS

As counsel for the College, the writer, at the invitation of the Board of Regents, attended a highly important and successful interim meeting which was held at the Town House in Kansas City, Kansas, on Saturday and Sunday, November 29 and 30, 1952. All Board members were present with the exception of Dr. Stephan Epstein who found it impossible to attend. Dr. Fred W. Wittich, Secretary-Treasurer, was also present. A number of matters of major importance were on the agenda and these were all disposed of under the very efficient gavel of Dr. J. Warrick Thomas who presided at this executive session. At the suggestion of the President, I shall review briefly the more important matters of business transacted at this meeting.

During the past several years there has been an increasingly heavy accumulation of business on the agenda of the annual meeting which has required the Board to remain in continuous session for from two to three days, and by reason thereof none of the Regents has found it possible to visit the exhibits and to give the several exhibitors the time and interest, as well as the encouragement, which many feel are properly due them. It was the unanimously expressed feeling of the Board that there was only one way in which to correct this situation and that would be to make definite provision for the holding of an interim meeting in each year at a location to be selected by the President, and which is best suited to the convenience of the greater number of the Regents. The majority felt that a date approximately midway between annual meetings would be preferable, but that in any case it should be held not less than four months before the date fixed for the next annual meeting. To relieve the heavy congestion of business at these annual Board meetings, it was agreed that this interim meeting must always be an executive session and the principal gathering in each calendar year for the transaction of business. To accomplish the purposes which Board members had in mind, it became necessary to amend Article V, Section 5 of the By-laws in the manner hereinafter set forth.

Prior to the Kansas City meeting, there had been increasing expressions of dissatisfaction with, as well as considerable criticism of, the haste with which the Nominating Committee has heretofore been required to act under and pursuant to Article V, Section 7, Subdivision (g) of the By-laws which covers the creation of this Committee and its functions. The Board felt that certain changes must be made so that instead of being forced to act within a few hours after its appointment, this Committee would actually be required to take time for a more thorough and careful study of all available personnel before making a final selection and announcing the official ballot. It was pointed out that through no fault of their own, committee members were required to act in such a comparatively short time that the official slate did not always carry the weight it should. Being hurriedly selected and generally on the last day when everyone on the committee was busy with last minute "goodbyes" and anxious to get started in the direction of home, the first names that came to mind were too often selected, with little or no thought being given to a full appraisal of the fitness, capacity, accomplishments in allergy and the availability of many who are regularly overlooked. Of necessity, time would not permit more than a purely perfunctory consideration of these qualifications since the official ballot had to be so hastily selected. On the other hand, if the Committee were actually required to take more time for its deliberations and

in making its final selections, the Regents were convinced that a slate would be chosen composed not only of those best qualified to serve but at the same time one which would represent with greater fairness all geographic areas. To accomplish this objective, it became necessary to make a further amendment to our By-laws, and accordingly at this meeting they were amended in two respects as follows:

Article V, Section 5 entitled "Regular and Special Meetings" has been amended to read as follows:

The Board of Regents shall hold at least one annual meeting and one interim meeting in each calendar year. The interim meeting shall be held at a time and place to be fixed by the President, but not earlier than six (6) months following the last annual meeting and not less than four (4) months before the date fixed for the next ensuing annual meeting. It shall be the principal business meeting of the year, and shall always be an executive session. Special meetings of the Board may be convened at any time by the President, or on a request made to him in writing and signed by no fewer than seven (7) members of the Board of Regents. Notice of the time and place of each meeting shall be given by mail or by telegram, addressed to each member of the Board either at his residence or place of business as the same may appear on the records of the College. In the case of annual and interim meetings such notices shall be given not less than twenty (20) days, and in the case of special meetings, not less than ten (10) days, prior to the dates fixed for such meetings.

Article V, Section 7, Subdivision (g) entitled "The Nominations of Officers" has been amended to read as follows:

The Nominating Committee shall be composed of five (5) members: the retiring president, two (2) members of the Board of Regents, and two (2) members of the College-at-large selected by the Board. It shall convene within twenty-four (24) hours after its selection; thereafter and not earlier than ninety (90) days but not more than six (6) months following its selection, the Nominating Committee shall select one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those selected. Any and all information contained in the membership records maintained in the Secretary's office as to any selectee shall, upon request, be seasonably supplied to the Committee. As soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary-Treasurer, provided said additional nominations are received in the office of the Secretary-Treasurer at least thirty (30) days prior to the next annual meeting. No nominations shall be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting.

Following a lengthy and thorough discussion of the entire Editorial Board set-up, consideration being given to the report prepared and submitted by the past presidents, a committee of three was named to review carefully the Editorial Board personnel, to study changes suggested in the editorial set-up as well as changes proposed in the format and numerous other matters looking toward the further development and continued growth of the ANNALS. This committee was given definite instructions as to the action the Board believed should be taken and it was instructed to report its findings to the Board at the forthcoming annual meeting in Chicago in April when final action will be taken on the editorial set-up.

Provision was made to set up a new International Committee as well as a Committee on Standards for Allergy Clinics. To assure proper representation to men subcertified in other specialties the latter committee was instructed to form a liaison with a similar committee which has been set up by the Academy.

The establishment of so-called "affiliate" memberships was thoroughly and completely discussed and considered. Being continually reminded by members in foreign countries that the existing differences in the monetary exchange rates in their currency and ours makes the payment of their dues an increasing hardship, it was decided to do something for these people rather than suffer a loss of foreign members whose friendship we greatly value while we are at the same time mindful of the prestige which their affiliation brings to the College. In the future, when, in the opinion of the Secretary-Treasurer, a real hardship appears to exist, he is authorized to determine how far the dues of foreign members shall be adjusted downward, although he has been definitely instructed that they are in no case to be reduced to a figure less than 50 per cent of that now being charged. The dues as finally adjusted are to include, in every case, the subscription cost of the ANNALS.

Mr. Reuel Estill of the Reuel Estill Company, New York City, came to Kansas City to address the Board on the subject of the establishment of a Foundation for Allergic Diseases, and in connection with a very illuminating discussion on this subject he distributed bound printed copies of an exhaustive study compiled by his organization at the request of the Academy.

Mr. Estill answered numerous questions put to him by Board members and was finally advised that no action would be taken at this time other than an expression by the President of our complete confidence in the proposed Foundation. He was told that before the College would join in the establishment thereof it must first be given assurances that it would receive equal and fair representation with the Academy so far as the naming of trustees and the selection of a joint committee and other matters are concerned. Thereupon, Mr. Estill stated that his organization had already made the announcement to the Academy that it would not be interested in going ahead with the work of raising funds except upon the definite understanding, which they considered fundamental and primary, that the College be given equal representation with the Academy on all matters connected with the establishment and operation of such a Foundation.

The Board unanimously endorsed a plan of group insurance for its membership after listening to Mr. Joseph K. Dennis of Life Associates, Inc., Chicago, who also came to Kansas City to address the meeting. After Mr. Dennis had fully discussed the terms of the contract of insurance written by his company, its costs and advantages, and after he had answered numerous questions connected therewith, his plan of group insurance was fully endorsed. Literature covering the same will be sent to all members and those who wish to avail themselves of the plan will now be free to do so.

Because of the ever-growing difficulty in getting satisfactory accommodations and dates, unless arrangements are made years in advance, the Board decided that our annual meetings in odd years shall be held in the city of Chicago, either at the Conrad-Hilton Hotel or the Palmer House, with meetings in even years scheduled to be held in other cities to which we may be invited; final selection of such cities to depend of course, upon our being able to have entirely satisfactory facilities available to us in every case; these meetings to be held at dates to be finally fixed by the Secretary-Treasurer, not however, earlier than the first week in April or later than the fifteenth day of May in each year, depending, of course, upon his being able to schedule a satisfactory date within that period.

It should be noted that henceforth the College will discontinue attaching

the names of all Regents to membership certificates, because this requires expensive new plates to be made up each year, and we will now, in the interests of economy, follow the almost universal practice of other societies and only the signatures of the President and Secretary will henceforth appear on such certificates.

Finally, in writing this report I was asked by the President to call to the attention of all members an increase in the dues which was made effective as of January 1, 1953. By resolution, unanimously adopted, the dues of Active Fellows were increased to $40 per year and the dues of Associate Fellows were increased to $30 per year. The Secretary-Treasurer asks that members please keep this in mind when they receive their statements from his office covering the dues currently payable for the calendar year 1953.

Typewritten minutes of this meeting, complete and in detail, setting forth verbatim the appropriate resolutions adopted by the Board in the transaction of the several matters of business reviewed above, as well as all other matters of business transacted in said meeting, have been prepared by the writer and may be found among the bound minutes in the permanent record book of the College.

ELOI BAUERS, *Counsel*

SECOND ANNUAL SYMPOSIUM ON BLOOD

Evidence that females, as well as males, can have hemophilia was presented at the Second Annual Symposium on Blood sponsored by Wayne University College of Medicine, January 17, at Detroit.

Two scientists from the Massachusetts Institute of Technology described the molecular weight and other physical and chemical characteristics of prothrombin. In another original report, two scientists from Wayne told of comparing properties of prothrombin as obtained from human and bovine plasma.

Other papers dealing with various other blood subjects were presented by scientists from the Wadley Research Institute and Blood Center, Dallas; University of North Carolina; University of California; Jefferson Medical College of Philadelphia; Atomic Energy Commission at the University of Michigan; Henry Ford Hospital; Mayo Clinic; University of Leeds; Ohio State University; Mercy Hospital, Baltimore; and the University of Southern California.

The purpose of the symposium was the "cross-fertilization of ideas from one specialty to another."

Progress in Allergy

HAY FEVER

A Review of the Literature of 1951

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FOREWORD

Each year the authors of this review hope for a glimmer of scientific light which will eventually lead us to the basic understandings in our field of allergy. Much has been written in every language and from many countries; however, in contrast to our previous reviews, many of the references listed in the bibliography are not reviewed. Many articles have been written which add little to the knowledge of our particular subject. Many others only confirm that which is already known.

This year the outstanding contributions deal primarily with the effects of the adrenocorticotropic hormones and cortisone in relation to hay fever —perennial and seasonal—better known as allergic rhinitis.

To date, every "miracle drug" discovered in the last five years, instead of curing, has served only to confuse the allergy problem. No drug has yet been discovered which will change the allergic constitution and effect a cure. Further research in the basic altered physiology and chemistry of the allergic individual must be done and understood before further drug development.

IMMUNOLOGY

The chemical immunological status of pollen still needs much work in order to clarify the confusion which exists among those who are interested in this subject. Recently, studies utilizing chromatographic analysis of pollen extracts have given us another avenue of investigation which may help to clear the existing confusion. Bernstein, Mosher and Mariella,[12] using a simple adsorption process, fractional chromatography and chemical analysis, were able to separate short ragweed pollen into several fractions. Some of these fractions were highly pigmented and irritating. For testing, the pigments of all fractions were removed and possibly some of the irritating substances. These white fractions all proved definitely antigenic. All the fractions were white, hygroscopic solids, which were completely soluble in water and reacted positively to the Molisch test for carbohydrates. Benedict's test was positive only after hydrolysis. The starch-iodine test was negative, and all fractions except the first gave a positive biuret reaction.

Activity of the colorless fractions in producing reactions was determined in ten ragweed-sensitive subjects by using serial scratch tests. The reactions were compared with those produced by similar nitrogen dilutions of the original unchromatographed extract. The nitrogen content of the weakest solution producing a reaction in each subject was determined for each fraction and the original extract. Some fractions gave reactions when the unchromatographed extract containing an equal or larger amount of nitrogen did not. The authors intend to treat patients with these fractions, observing clinical results and incidence of reactions, as compared with

ordinary ragweed extracts. They also plan to extend their work to food, dust and molds, et cetera.

Dankner et al[32] reported their studies using chromatographic fractionation of short ragweed extract. A minimum of six different active components was obtained from low ragweed pollen. Five of these were of relatively small molecular size; four were peptides, and the fifth was a carbohydrate. All of them were diffusible through a Visking membrane. After six days against running water a highly active fraction was retained within the membrane containing at least one large polypeptide or protein. The activity of each fraction was demonstrated by direct intradermal test in ragweed-sensitive subjects and by passive sensitization and neutralization studies.

The authors unfortunately had insufficient amounts of each extract to perform sufficient serial dilution skin tests to properly evaluate variations within different individuals.

The authors report work in progress on their present study of ragweed extract by paper chromatography. We hope to be able to report further in next year's review.

Perlman[107] reports a similar study using chromatography. He demonstrated a large number of allergic components in crude extracts of ragweed pollen. Using the scratch test he was able to demonstrate at least two fractions producing positive skin reactions when tested on ragweed-sensitive patients.

Stevens, Moore and Baer[141] studied the amorphous precipitate of giant ragweed extracts formed in solution on standing in the cold. They were able to refine and crystallize fine yellow needles of isoquercitrin. The freshly prepared amorphous material showed biological activity which was entirely absent in the crystalline material. The pigment is a very actively moving substance in the electrophoretic field. Crystallization removes the nitrogenous content from this amorphous substance and diminishes biologic activity fourfold until the pure crystalline material is no longer able to give cutaneous reactions. The nitrogenous material may be combined with the amorphous pigment, thus being responsible for the skin activity.

Loveless, Wright and Ryan[96] report their further studies on allergenic fractions of low ragweed pollen. This article deals with the immunologic, electrophoretic and chemical characteristics of diffusates. An appreciable proportion of the large losses of nitrogen and carbohydrate from low ragweed extract during extensive, conventional dialysis through cellophane might be due to the breakdown of larger into smaller filtrable forms. This is now believed to be 10 per cent for the nitrogenous materials and about 30 per cent for the carbohydrates. Whereas all ragweed-sensitive patients reacted to the nondiffusible constituents, at least 20 per cent were unaffected by the diffusates in the extensive tests of the skin, eye and serum. Also studied were diffusates by phosphotungstic acid-precipitable nitrogen (PTA-N) methods, as well as by electrophoresis. They concluded that diffusates were not only less frequently allergenic than whole extracts, but were also less efficient as immunizing agents in the production of thermostable antibodies and of chemical resistance. This confirms the work of Stull and his associates, but is in disagreement with that of Abramson and Rockwell, who held that molecules of about 5,000 molecular weight are the chief allergens of ragweed pollen.

Stevens, Moore and Gelston,[142] reporting their major electrophorectic component studies on giant ragweed, discuss particularly the molecular

weight and chemical and biologic characteristics. The authors refer to the work of Abramson and his associates who describe electrophoretic patterns of whole ragweed extracts, certain grasses and tree pollens. A slow-moving unpigmented fraction was found in each which, after separation in the cell, was extremely active when tested in the skin of sensitive patients. Also found was a rapidly moving pigment of minor importance. Between these two were boundaries of other pigmented substances, all moving toward the negative portion of the cell. The rapidly moving pigment has been identified as isoquercitrin. These authors studied extracts retained within a Visking membrane with a calculated average pore size of 2.5 Å. When giant ragweed extract was dialyzed, about 85 per cent of the nitrogen passed through the membrane. The concentrated material within the sausage was light brown in color, and almost one half was precipitated by saturated sodium sulphate, while only 3 per cent of the nitrogen in the dialysate was precipitated by this chemical. In some experiments when extracts were dialyzed at 4 degrees for ten to fifteen days, isoquercitrin crystals actually formed within the substance of the membrane, causing slow leaks. The molecules composing the material within the membrane had molecular weight of about 18,000 and appeared to be elongated, with a ratio of length to breadth of 14:1. The authors were concerned only with the slowly unpigmented fraction, not the isoquercitrin. Comparing the patterns of the whole extract, the dialysate and the concentrated material resulting from the long-continued dialysis of the extract showed a component with the same mobility as described by Abramson in all three, and this is the only component occurring in the pattern of the material within the bag. The authors feel that the component in the pattern of the whole extract is largely a mixture of nitrogen containing molecules of various weights, all with the same mobility.

Hay fever patients have been successfully immunized with the concentrates. Preliminary observations indicate that, per unit of total nitrogen, injections of the concentrates of ragweed pollen extracts appear to be superior to injections of the whole extracts for prevention of hay fever.

Arjona, Segovia, and Martinez[6] studied microprecipitins and blocking antibodies after specific therapy. They noted an increase of blocking antibody titers and threshold of skin reactions after treatment, coinciding with clinical response.

POLLEN AIR STUDIES

Atmospheric Studies

Durham,[112] as chairman of the pollen survey and herbarium committee, reports certain interesting facts at the time of the committee's report in November, 1951; pollen counting was still in progress in some of the southern cities, so that the report was somewhat incomplete. They noted that interest in pollen surveys was spreading to more distant parts of North America, and even to Europe and Asia. Many studies were made in Alberta and several Canadian National Parks, including Lake Louise and Banff, and fifteen new local ragweed surveys were reported from maritime provinces. One atmospheric test series was carried out in the Virgin Islands, and field checks were made in Puerto Rico, Hispañola, Jamaica and Cuba. In addition to the previous fifteen stations of last year, Florida had seven new locations in 1951. Detroit carried out an intensive ragweed study involving twenty-three locations. Of special interest was the work done in Wenatchee Valley, Washington, where short ragweed

has spread rapidly in the orchards in recent years. At Medicine Hat in southeastern Alberta, ragweed has gained its only known foothold in Western Canada. In Florida, only Tampa seemed to be making a bad record in 1951.

In the Great Lakes area, there was a decided increase in atmospheric ragweed pollen as compared to 1950, a very light year. In this area the apex of ragweed concentration occurred in almost every city within two days of the end of August.

Spiegelman and Blumstein[140] studied pollen counts on different areas of the same slides and on other adjacent slides. When subjected to critical statistical analysis, a high degree of correlation was found between any and every one of these areas, regardless of the direction in which the slide was placed, or the slide area which was counted.

Shapiro and Rooks[134] studied slides exposed in ten different sites of a residential community in a large city (a known high ragweed pollen area) and compared results with a centrally located sampler. They conclude that on a seasonal basis there would be little accomplished by local ragweed control measures.

Surveys made by Sherman and Gay[135] in the Maryland area with the usual accepted techniques revealed variable counts. The use of different apparatus seemed to make very little difference since they all showed similar trends.

In the Rio de Janeiro area pollen counting was done by Bernd and Oliveira Lima.[10] Their report indicates the presence of cypress and grass in September and October, amaranths in November, and chenopods in December. This was the same for Porto Alegre, Alegrete, and Passo Fundo. They found the Compositae family to be an insignificant problem.

Tree pollens, surveyed by Claus and Smoldone[26] in Western Pennsylvania, revealed the following to be present in March and April: alders, American elm, hazelnut, poplars, and red maple.

Walton[162] of the Winnipeg Clinic reported on air-borne allergens in Western Canada. He recommends the use of specific allergens for desensitization.

Schleinzer[129] tested forty patients with proved pollen extracts during a pollen-free period. The tests were conducted in a temperature- and humidity-controlled room while the patients were at rest and in a fasting state. Alveolar oxygen, carbon dioxide tensions, arterial oxygen and saturation, and rectal temperatures were recorded throughout the experiments. Thirty per cent of the patients studied revealed a striking decrease in the arterial oxygen saturation and a decrease in rectal temperature of from 0.2 to 1 degree. There was an increase of the respiratory minute volume, associated with a decrease in the depth of respiratory frequency.

Prince[113] noted some of the more common miscellaneous allergens which might be incriminated in the etiology of erratic and seasonal allergy. He suggested that such items are of occasional importance in the treatment of seasonal hay fever.

Estrada de la Riva[42] points out that due to the high humidity in Cuba the total pollen count is very low; however, he found the mold content to be rather high, including Hormodendrum, Mucor, Fusarium, Rhizopus and Aspergillus, in decreasing frequency.

The role of fungi in allergy was studied by Bocobo.[14] Targow and Plunkett[147] made an extensive five-year survey of the atmospheric incidence of fungus spores in the Los Angeles area. They identified some sixty-odd

genera and families, of which twenty-seven were of frequent occurrence. About one third of these showed no seasonal variation. The predominating spores were those of Hormodendrum and Alternaria. In the Savannah area, Griffith[66] found fungi to be an important causative factor of clinical symptoms from April to November, varying with the season.

Heise[77] previously had shown certain algae to be a cause of hay fever in susceptible persons. Intracutaneous skin tests, passive transfers, and specific hyposensitization were carried out with relief of symptoms. He collected algae of an entirely different morphology from a Wisconsin lake, and found that despite their apparent differences from the first group reported, both belonged to the Myxophyceae and both possessed the same antigenic characteristics.

Spores of *Lycopodium clavatum* (moss) were reported as a cause of allergic rhinitis by Salen.[124] He noted that they may occur seasonally and also when in contact with a pharmacy. The powder is used in certain industries.

MacFarlane and Cecil[97] drew attention to the use of Pilot's fluid for eosinophil counting, rather than the one recommended by Randolph, claiming that the former is much easier and quicker. Florentin et al[49] reported on the pollution of the atmosphere in certain French cities, while Froucht-man and Fosten[58] made similar studies in Barcelona.

Zivitz[171] presented a most interesting study concerning the effect of climatotherapy on allergic individuals in the Miami area. He feels that this area is a haven for ragweed-sensitive patients. One hundred fifty persons were studied from June through October, during which time occasional twenty-four-hour pollen counts of 8 or more granules per sq. cm. were noted. Inland from Miami more were encountered. Patients coming to Miami because of tree-pollen allergy do quite well because of the prevailing ocean breezes during 80 per cent of the year. Grass-pollen sensitivity, due mainly to Bermuda and Johnson grass, extends from February through November with relatively low counts prevailing. Mold allergy in Miami has not yet been completely explored, although Alternaria is infrequently found. The most common fungus spores are Mucor, Monilia, and Rhizopus. The author points out that Miami is a good haven for patients; however, it seems that the value of climatotherapy is acclaimed during the early transition period only, and that relapses occur in from four months to five years, the average latent period being two years. Individual, specific hyposensitization must then be instituted for relief of symptoms. This author sets up certain criteria for climatotherapy in Miami and believes it to be primarily adjunct to specific therapy.

DIAGNOSIS

Wiseman[165] discusses the comparative skin results by testing in the antecubital and popliteal spaces. Skin tests with histamine in both atopic and nonatopic individuals cause larger reactions in the antecubital fossa than elsewhere on the arm. There was a similar but even greater reaction in atopic patients when tested in the same manner with allergens to which they were sensitive. This was found similarly true when using the popliteal space for testing. This has been observed by many and is nothing new.

Peshkin[108] has an excellent presentation of the interpretation of allergic skin tests. This was given in conjunction with the First International Congress of the International Association of Allergists, held in Zurich, Switzerland.

Theodore[151] advises the use of epithelial scrapings of the conjunctivae. He feels that this method is especially beneficial in diagnosing allergic conjunctivitis by the amount of eosinophilia noted and will also alter the prognosis and management of these cases.

Mulligan[104] reports the occurrence of intense pruritus of the vulvae in conjunction with pollinosis. Hyposensitization brought about marked relief.

Poos[111] reviews the mechanism of allergic reactions as they occur in the eye. Mention is made of the reactions occurring in hay fever.

Glaser, Kaiser and Siegel[60] discuss hay fever as a public health problem in children. In Rochester, New York, Glaser et al noted that in school children 8.3 per cent suffered from ragweed pollinosis in the first grades of school. This causes much absenteeism, and the authors feel this constitutes sufficient reason to delay the opening of school for a short time after Labor Day, which is usually the height of the hay fever season in this area.

A number of articles have been reported in which the rôle of infection in relation to pollinosis and rhinitis is discussed. Thomas,[152] McLeod,[100] Melchior,[101] Hermosilla and Ricchetti,[78] Denhow, and Grove[68] discuss many of the diagnostic problems involved in rhinitis as related to seasonal symptoms.

Davison[35] points out the rôle of food sensitivity in the production of seasonal nasal allergy. In his studies, he found that 16 per cent of all patients with nasal symptoms in some particular season only had symptoms produced by foods. In patients with severe seasonal symptoms, but minor perennial symptoms, 36 per cent were food sensitive; in patients with perennial symptoms only, 25 per cent; and in patients with perennial symptoms with seasonal exacerbations, 44 per cent. Consideration of detailed food sensitivities may make the difference between a fair and excellent result in the outcome of their therapy.

Criep and Riley[31] discuss a case of paroxysmal rhinorrhea and nasal obstruction. The symptoms occurred at work and were usually associated with the handling of a preparation containing agar. Skin tests were positive to the agar as well as to the floor sweepings. Passive transfer and inhalation tests were also positive.

TREATMENT

An interesting and whimsical dissertation on nasal function and neurosis was presented by Brown[19] and would make good reading. No advances of note in the general therapy of hay fever were apparent in the literature this year, however, some of the articles on management are noted below.

Schaffer and Seidmon[127] wrote an excellent, concise epitome on the management of allergic conditions of the upper respiratory tract. They felt that at least 50 per cent of adult allergy had its origin during childhood; therefore, early diagnosis as well as adequate and complete therapy and control will reduce the incidence of upper respiratory tract allergy in the adult population. Hay fever represents about 45 per cent of respiratory tract allergy. Results in children are usually gratifyingly good, and treatment must cover a long period of time. We heartily recommend this article to all general practitioners interested in allergy.

Ratner et al[120] studied a series of 750 children with dermal (urticaria, eczema) and respiratory (perennial and seasonal hay fever, asthma) manifestations of allergy. Both dermal and respiratory evidence of allergy was

found in 35 per cent of the children, respiratory symptoms only in 41 per cent, dermal syndromes only in 22 per cent and other allergic syndromes in 2 per cent. Fifty-nine per cent of all patients with eczema or a history of eczema developed respiratory allergy, with hay fever occurring by the sixth or seventh year. The authors believe that thorough treatment will prevent the development of respiratory allergy in children with allergic dermatitis.

A comparison of the results of anamnestic and perennial therapy was attempted by Abram and Frankel[1] in the treatment of pollinosis. The former group consisted of patients who had had at least one full year of perennial treatment and were then given up to six booster injections only, prior to the onset of the next season. Although no protocols were included, they felt that anamnestic therapy resulted in quite adequate treatment as compared with the previous perennial year. This is a very interesting observation, which, due to varying circumstances, we have also noticed on occasions. However, a much more detailed and larger series should be evaluated since so many variables, too numerous to mention, not infrequently influence the results of therapy.

A general discussion of the present status of pollen injections was presented by Waldbott.[161] He described and gave his methods of specific desensitization in pollinosis, including preseasonal, seasonal and annual therapy. Brief reviews of the orthodox methods of the management of hay fever were reported by Taub[148] and Slepian[139] in the *Eye, Ear, Nose & Throat Monthly*.

An excellent bibliography on the relationship between pollen therapy, clinical results, and methods for classifying such patients was presented by Shahon et al.[133] Their study of [100] ragweed hay fever patients showed no absolute proof that there exists any definite relationship between massive pollen therapy and the reduction in the size of the wheal on intracutaneous testing after a period of three to four years of treatment. Clinical relief was noted in patients receiving massive doses of pollen therapy when maximum doses ranged from 5,000 to 10,000 PN units, given at three-week intervals perennially. The reduction in the size of the wheal upon retesting, after more than one year of perennial treatment, was not definite indication of the degree of improvement elicited by these patients.

Present-day concepts concerning the etiology and treatment of allergic states are summarily discussed by Goodman.[63] No aspect is gone into in much detail; however, one statement worth repeating is that asthma develops in approximately 30 per cent of the patients with allergic rhinitis, and it is unwise to rely on symptomatic treatment alone (e.g., antihistamines), even though it is effective. Ratner[119] gave a general review of the management of hay fever in children, with special emphasis on subcutaneous desensitization.

Naterman[106] used suspension of pollen tannate in peanut oil with 2 per cent aluminum monostearate added. The methods of preparing such suspensions were described. He felt that the advantages of using this suspension depend on slowing and prolonging the absorption of the active materials, resulting in (a) increased safety and tolerance of larger doses, and (b) increased stability of the active material due to its dehydrated state, and possible elimination of enzymes. The author usually began with 0.05 cc to 0.15 cc of a 1:1000 dilution and reached a final dose of 0.1 cc to 0.3 cc of a 1:1 suspension obtained with an average number of 4.3 to 7.4 injections, with 90 per cent satisfactory results.

Some common misconceptions in allergy therapy were enumerated by Feinberg[44]; namely, that positive skin tests indicate clinical sensitivity; that negative skin tests indicate the absence of such sensitivity; that desensitizing treatment sets can be made up on the basis of skin tests alone, without clinical evaluation; that desensitization is a short-term course of therapy; that nonallergic factors can be ignored in allergic disease, and that antihistamines and ACTH are the newest and best forms of therapy. Schenck[128] feels that perennial and seasonal nasal allergies contribute to infections of the upper respiratory tract, and therefore must be treated, not merely for their own sake, but also to prevent acute and chronic infections with their train of serious sequelae.

A report by Gouze[64] was presented in which forty-five patients with hay fever or allergic rhinitis received Clopane in doses of 25 to 50 mg two or three times daily. All except five experienced satisfactory relief of nasal congestion by diminution of secretions and constriction of the swollen and edematous turbinates. No protocols were included. Some patients were given this preparation in conjunction with an antihistamine, Histadyl, and it was this observer's opinion that a synergistic action existed with minimal side effects. Thacker[150] reviewed the nonspecific therapeutic methods applicable in nasal allergy, and feels that at times these in combination with specific measures are indicated. Leake[91] gave a very comprehensive lecture on drugs used in allergy, which was reported in the *Letters of the International Correspondence Society of Allergists.*

In reporting on a study of 434 patients hospitalized for asthma over a fifteen-year span, Baldwin, DeGara and Spielman[8] noted that the greatest admissions occurred from July through September, during the air-borne pollen season, which seems to be an important factor in causing hospitalization in asthmatics. This was a carefully conducted survey, including the various etiologic factors (infection, psychosomatic, allergic, et cetera), structural changes, cardiac status, mortality, therapeutic measures, and hospital management. A very complete review of the therapeutic substances employed for the relief of asthma was presented by Herschfus et al.[80] Much of this information might be applied to this common complication of hay fever.

One other comment on the treatment of hay fever was in the article by Gay and Gay[59] in which it would appear that their regime was not very effective for hay fever.

MISCELLANEOUS

Wittich's[166] "Allergy in retrospect and its future," published in the *International Archives of Allergy and Applied Immunology,* gives a very excellent history of hay fever.

Forman[52] reports his views on the basis and principles of allergy. It is a clear, concise presentation of a very difficult subject which is full of controversies.

Brandenburg[18] discusses allergy as a disease of adaptation. Explanation for pollinosis requires additional factors.

Halpin,[72] in a special article written for the *Quarterly Review of Allergy and Applied Immunology,* discusses the military status of the allergic patient. In regard to hay fever, a physician certifies that a patient who suffers from severe seasonal hay fever with asthma is disqualified for the military.

Halpin's[73] "Miscellaneous review of allergy literature" contains much information in relation to allergy and some phases of seasonal rhinitis especially due to fungi. This review, among others, is well worth reading.

PSYCHODYNAMICS

Very few papers are reported this year in which pollinosis is markedly affected by the psyche. Murray and Bierer[105] reported a case of prolonged sneezing in an allergic child with presumably controlled symptoms. The continuous sneezing was due to a situational basis resulting in a marked emotional imbalance.

Holmes, Trueting and Wolff[82] give evidence of summative effects exhibited in patients with hay fever due to life situations, emotions and nasal disease.

THE ANTIHISTAMINES

The plethora of articles on the antihistamines has apparently abated. As with so many much-vaunted new preparations, after the initial impact, they are now taking their place as a useful addition to the armamentarium of those allergic syndromes in which they are indicated.

There were a number of excellent papers on the general subject of the histamine antagonists, and the reports follow.

Sherman[136] discussed the use of the various antihistamines in the treatment of various types of allergic disorders and their relative value in alleviating the symptomatology of many other conditions. The author suggested a classification of these drugs in order to facilitate the best utilization of each one for maximum therapeutic benefits, and stressed the fact that these drugs are not curative and have very uncertain actions.

A very complete study of the use of various antihistamines in children was made by Stoesser.[143] The information quoted is that obtained in a study of 4,561 children over a period of five years. The choice of antihistamines in various allergic syndromes, based on this experience, is tabulated. An excellent general discussion of the histamine antagonists was presented by Swineford.[146] In this article he discusses their uses, side reactions, complications, mode of action and limitations. The basic pharmacological principles are enumerated, and the reasons why these compounds are not panacea for allergic disease are presented.

Burrage[22] reviewed five years' experience with antihistamine therapy, and felt that it confirmed the value of these preparations in many types of allergic disease, as well as in other manifestations based on histamine action. Practical details concerning selection, dosage, side effects and toxicity of the antihistamines were discussed. A review of the therapeutic application of the antihistamines was reported by Farrar,[43] who felt that they provide good symptomatic treatment for a variety of disorders. These drugs seldom cure anything, but their use often makes the patient comfortable and, in some instances, prevents secondary complications and shortens the course of the illness. The dose is the one that controls symptoms without undesirable side effects. Shure and Harris[138] evaluated drugs used in the management of allergy, discussing at some length the various antihistamines.

Dannenberg and Feinberg[33] presented an article on the development of tolerance to antihistamines. Of a series of patients the majority showed evidence of this tolerance, as shown by failure or diminished effectiveness of the drugs to reduce the wheal and flare response to histamine and rag-

weed extract. The time required to develop tolerance varied from seven to twenty days on therapeutic doses. Tolerance to one antihistamine extended to others, even though the chemical relationship was not close. The return of pharmacologic response after discontinuing the drug took from three to fourteen days.

A few papers on specific antihistamines have appeared, among which are the following. Thomas and Kelly[153] made a clinical appraisal of a new antihistamine drug on 100 private patients, five of whom were hay fever patients. Satisfactory response was recorded in two. Once again as in most clinical papers reviewed by us, protocols were lacking. Thirty-four normals and 296 patients treated with Ambodryl were studied by McGavack et al.[99] They demonstrated the following pharmacologic action: the suppression of the "wheal and flare" reaction which normally follows the intracutaneous introduction of histamine; a tendency to pupillary dilitation in doses of 300 mg or more daily; and slight lowering of the basal metabolic rate in the largest doses.

In daily doses of 75 to 600 mg orally for periods of time varying from one to fifty-four weeks, Ambodryl produced no appreciable changes in weight, pulse rate, blood pressure, electrocardiogram, icteric index, van den Bergh reaction, cephalin flocculation and many other chemical studies. About 90 per cent of all cases of seasonal allergic rhinitis obtained relief. Side effects or toxic symptoms occurred in 8.4 per cent of 321 subjects, many of whom had syndromes other than hay fever. No untoward reactions were noted in daily doses below 100 mg. The unpleasant side effects included drowsines, dryness of the throat, diarrhea and anorexia.

A pharmacological study of Antistine by Craver et al[30] indicated that it was an active antihistamine of low toxicity. An interesting study by Landau, Nelson and Gay[88] showed that procaine and Stovaine had an antihistaminic effect about one hundredth as effective as Benadryl. On the other hand, antihistamine compounds had two to twenty-five times as much anesthetic effect as procaine in human skin. In a report on "repeat-action" Chlor-Trimeton tablets, Wittich[167] felt that they were effective in the symptomatic treatment of various respiratory allergies. Seidmon[131] obtained good results in most of his seasonal rhinitis patients (numbering seventy-seven in all) using regular Chlor-Trimeton. The dosage in the majority of the patients was 4 mg three times daily. Side effects were mild and occurred in 30 per cent of all cases reported upon.

Peshkin, Rapaport and Grosberg[109] employed Phenergan as an adjunctive drug to specific allergy treatment in 193 allergic patients. Approximately 100 of these had either hay fever alone or in combination with other allergic manifestations. They obtained satisfactory response in thirty-seven patients and moderate in thirty-eight. It was obvious that when hay fever occurred alone the results were better than when it occurred in association with other allergies; however, it isn't too apparent from this report that this drug was particularly efficacious. In general, the therapeutic response was better in children than in adults, and the incidence of side reactions was also significantly less. Our personal experience with this preparation has been mostly in patients with perennial rhinitis, particularly children. It has been our impression that in children Phenergan is a valuable drug that proves to be quite effective when given twice daily.

Numerous reports on the toxic side effects of the antihistamines appear in the literature, some of which follow.

An excellent review of the toxic effects of the antihistamines was presented by Wyngaarden and Seevers.[168] The common side effects of these agents were tabulated with brief comments thereon. Most of them are relatively innocuous and are important merely because they are annoying to patients; however, certain patients have severe side effects and much unpleasantness. Serious reactions have resulted from idiosyncrasy or from overdosage. Eleven fatal cases were reviewed, eight of whom were children under two years of age. Infants and children were predisposed to convulsive seizure from overdosage; the mortality rate in these patients is very high. Adults tend to develop a central nervous system depression, which may at times be lethal. Agranulocytosis is another serious development which may occur. The treatment of such reactions is at present purely symptomatic. It is imperative that all physicians be aware of the potential hazard of the antihistamine compounds, as well as their usefulness. Törnqvist[154] wrote of a two-year-old boy who after having been given 15 gm of an antihistamine, b-dimethylaminoethyl benzoylhydrylether hydrochloride, died in status epilepticus. Uhle and Knoch[157] presented a case of a male patient who was given Thephorin for the symptomatic treatment of hay fever; the patient experienced difficulty in expelling bladder contents following its use. This toxic symptom disappeared after the drug was withdrawn, with no toxic sequelae. They postulated that Thephorin by virtue of its anticholinergic action may have had this effect. Interestingly enough we have seen several cases of constipation following the use of this antihistamine preparation, which cleared promptly on discontinuance of medication.

Uvitsky[158] presented a case of purpura apparently due to the use of Pyribenzamine, and not to Benadryl. The authors observed that in the same patient, some of the antihistamines may cause purpura, while others will not; also that the dose of the drug used need not be excessive, nor need it be used for an extended period of time to produce this effect. Bradlow[17] reports a case of agranulocytosis due to Thephorin. The dosage employed was 25 mg three times daily for four days. Seven other cases in the literature are mentioned, five due to Pyribenzamine, one to Diatrin and one to 2339 RP. In the *Journal of the Maine Medical Association,* Glassmire[61] presented a case of fatal pancytopenia following the local use of Pyribenzamine cream, with the occasional use of Neo-Antergan orally. Although necropsy revealed the pancytopenia, its causal relationship to the use of the antihistamine compounds was not only adequately shown. Landes and Zuben[89] by using several objective tests could find no evidence of sedation with Neohetramine. In the Queries and Minor Notes of the *J.A.M.A.*[115] a question was asked as to whether contraindications existed for the use of antihistamines in hay fever patients with coronary disease. The answer given was that there was no apparent evidence of a deleterious effect on the coronary circulation from the use of such compounds.

ADRENOCORTICOTROPIC HORMONE AND CORTISONE

As was to be expected, 1951 saw a considerable increase in the clinical usage of these hormones, especially in allergic diseases. The basic physiology and modus operandi of each remains in the same general category, as established by previous investigators; however, the decision as to which one to use and the method of administration has been further clarified by the continued trials in certain specific diseases. The complications arising during administration of ACTH or cortisone, or after they have been

discontinued, stamp these hormones as potentially dangerous agents which must be fully understood before being prescribed by physicians.

These problems and others will be presented herein. So much has been written and so great a variety of reports has appeared in the literature during 1951, that a clear, concise, chronological report is almost impossible.

The effect of ACTH in pollen-sensitive patients has received much attention, with the hope that this method of therapy would give greater results than the presently accepted series of hyposensitization injections with specific pollen extracts. The reported results have been variable. Rappaport and his associates[117] noted clinical improvement in nine of twenty-six ragweed-sensitive patients who received 60 mg of ACTH daily for four days. Control patients who received placebo injections failed to improve. This group of workers also noted no change in the reagin titer nor in the skin sensitivity to ragweed pollen after ACTH. They suggest a correlation between the degree of skin sensitivity, the peripheral eosinophilia, and the tissue eosinophilia. They also found no change in the histologic characteristics attributable to the use of ACTH.

Zeller[170] selected eight patients who suffered from ragweed hay fever and bronchial asthma for treatment with ACTH. Generally, he found asthma to be relieved sooner and more completely than hay fever. This was also found by other investigators.

The use of ACTH in the treatment of ambulatory asthmatic patients was carefully evaluated by Brown and associates,[20] and found to be quite satisfactory. (Our own experiences parallel those of Brown et al in the treatment of the asthmatic patient, where this disease was accompanied by hay fever.)

Haxthausen[76] verified the oft-repeated study of the behavior of skin tests after ACTH therapy. He noted no distinct effect on skin test results.

Bowman, Siegel and Walzer[16] observed the effect of a single dose of ACTH on the atopic and histamine skin reactions and report a slight but definite depression effect of the hormone upon atopic cutaneous skin reaction. Most investigators do not agree that a significant measurable decrease occurs. Leith, Graham and Burrage[93] studied the effect of ACTH on the immediate skin reaction and also the passive transfer test in man. They treated ten hay fever patients with 20 mg of ACTH administered intramuscularly every six to eight hours for eight doses. They noted a subsidence of hay fever symptoms in four of these patients, but only temporarily. In the method and dosage used, they report no significant alteration in the scratch or passive transfer tests. The adrenal response to ACTH was demonstrated by a fall in circulating eosinophiles and a rise in urinary 17-ketosteroids.

The influence of ACTH on reactivity of the bronchial tree, skin and secretory glands to specific antigens, histamine and Mecholyl in bronchial asthma, was carefully observed by Grob and his associates.[67] They noted that 100 mg of ACTH had no effect on the histamine skin reaction in the nonallergic. Loveless[95] studied the influence of ACTH on the sensitizing and immunizing antibodies of inhalant allergy. She noted the effects of ACTH on the conjunctival susceptibility and serum antibodies in a young woman who suffered from intractable atopic dermatitis, as well as mild hay fever related to pollens and animal danders. Controlled tests on the fourteenth and twentieth days of hormone treatment revealed that con-

junctival tolerance for grass pollen had been raised sixteenfold, and four times stronger extracts of pollen and dog dander had to be used to produce the same pre-ACTH responses. The circulating sensitizing antibodies remained constant for the three allergens tested. Immunization with ragweed pollen failed to provoke any blocking antibodies; this was believed due to the fact that ACTH was administered only three and three-quarters hours beforehand. The author also suggests that ACTH also exerted a temporary inhibiting effect, since a larger-than-normal booster dose was accepted by the patient at the three and three-quarters hours point.

That ACTH must be gradually withdrawn, rather than suddenly stopped, is borne out by the work of Keeton et al.[85] These investigators observed two patients with respiratory impairment who revealed dramatic respiratory symptoms upon sudden withdrawal of ACTH. Both responded favorably to readministration of the hormone. Subsequent gradual withdrawal was accomplished without incident in one of the patients. These investigators suggest that withdrawal of ACTH in patients with pulmonary disease should be done with great caution.

Reactions to ACTH, since it is a protein, will probably be reported from time to time. Feinberg et al[46] relate an instance of severe allergic reaction to this hormone. The patient also showed reaction to all forms of corticotrophin and other pituitary preparations. The significance of the immunologic and clinical aspects of this subject is discussed.

Harris[75] noted that cortisone is useful in controlling prolonged periods of asthma which are resistant to other forms of treatment. Oral cortisone therapy in allergic diseases, as observed by Friedlaender and Friedlaender,[55,56] often revealed complete relief from acute symptoms. They administered up to 200 mg of cortisone by the oral route, and found that the hormone was readily absorbed from the gastrointestinal tract, and that in comparable dosages it will affect allergic diseases in much the same manner as intramuscular cortisone. These authors felt that improvement was more rapid with oral cortisone, but the therapeutic effect was dissipated more rapidly. They caution that patients must be closely observed in order to avoid the known side effects of hormone therapy.

Engleman et al[41] studied the use of oral cortisone suspended in syrup. They found that such mixtures remain potent for about one week, and that the hormone is rapidly absorbed from the gastrointestinal tract and is therefore particularly effective in acute illnesses. They noted that the minimal effective dose varies widely, but most patients have been maintained on 75 or 100 mg daily. They note that the effect of the orally administered drug is of short duration, thus permitting prompt termination when undesirable side effects occur. They noted only hypertension and Cushing's facies as the prime side effects. Salen[125] also reported on oral cortisone therapy, primarily in bronchial asthma.

As would be expected, local use of cortisone was observed by numerous investigators. Dill and Bolstad[38] used cortisone, diluted 1:4, in the nose of allergic rhinitis patients, and report effective relief in chronic cases, with reduction in nasal stenosis and post-nasal discharge, and a diminution in nasal polypi.

Zadunaisky[169] reports on local use of cortisone in hay fever and reports improvement in the nasal condition. Obstruction, rhinorrhea, pruritus, and irritation of the nasal mucosa was also relieved. This preliminary report warrants further investigation.

Sensitivity and other ill effects, as with ACTH, were not unexpected,

and they have also been reported. Bernstein[11] reported a patient, who after the first injection of 100 mg of cortisone intramuscularily developed complete nasal obstruction and wheezing, urticaria, and edema of the eyelids and cheeks. These symptoms responded to epinephrine. At the patient's insistence, she was given 50 mg of cortisone intramuscularly at a later date. Within five minutes she experienced a similar, but less severe, reaction. This patient had been receiving antihistaminic drugs at the time of both reactions.

The question of the status of oral cortisone in the treatment of hay fever and its danger during pregnancy appeared in the *J.A.M.A.*[116] The answer given was that results in hay fever vary, and that cortisone in such patients is probably not as effective as in asthma. Also, since this hormone tends to depress pituitary function and since this activity is an essential phase in the physiology of pregnancy, cortisone would be contraindicated.

Lowell and his co-workers report a patient who developed convulsive seizures during treatment with cortisone. After eleven days on such therapy, the patient developed seizures of unconsciousness preceded by headache and associated with nausea, vomiting, clonic convulsions and incontinence. His symptoms of severe bronchial asthma recurred, and cortisone (100 mg daily) was resumed, but proved less effective than during the first course. After three weeks, when the dose was gradually being decreased to 50 mg per day, tremor of the fingers and lid-lag were noted. Other findings suggestive of hyperthyroidism, including radioactive iodine uptake, were absent. The lid-lag and tremor disappeared when cortisone was discontinued. The possible mechanisms involved in this patient were discussed.

Death from asthma while using cortisone was reported by Zoss and Zodikoff.[172] Their patient, a severe asthmatic, had received ACTH at the start of therapy and was placed on oral cortisone after ten days. After five weeks of this therapy, the patient went to Denver, Colorado, where his asthma returned with such severity that death ensued within a few hours. Postmortem examination revealed the usual findings in deaths due to bronchial asthma, as well as a slight decrease in the amount of intercellular cortical lipoid and in the thickness of all the cortical layers.

Borman and Schmallenberg[15] report a patient who was usually euphoric, but who committed suicide following cortisone therapy.

The effect of ACTH and cortisone on certain immunologic mechanisms, including reversed anaphylaxis, was reported by Arbesman et al.[5]

Therapy of allergic diseases with either of the two hormones was observed by numerous investigators, all with essentially the same results.

Feinberg and his co-workers[45] studied the effects of ACTH and cortisone, and found them most effective in intractable asthma, acute status asthmaticus, and severe drug reactions. Three ragweed-sensitive patients who had previously had good results from specific hyposensitization yielded indifferent results with these hormones. None of the patients studied revealed any change in skin reactions to antigens and histamine after ACTH or cortisone.

Cooke et al[28] made similar observations and also noted that there is little lasting effect from therapy with these hormones when the causative factors continue to operate. These investigators carried out serologic studies using chemical and electrophoretic techniques. They found that the patterns in many sera showed abnormal distribution of the various

protein fractions, albumin, alpha$_1$, alpha$_2$, beta and gamma globulins. Immunologic studies indicated that symptomatic benefits and tissue alterations resulting from such hormonal therapy are not due to interference with the immediate whealing reactions. They also note that the skin-sensitizing antibody of allergic sera is not entirely contained in the gamma globulin fraction of such sera.

Seibold[130] evaluated therapy of certain allergic diseases with ACTH and cortisone and noted that all, including hay fever, have yielded symptomatically, but lasting relief was not seen. Seasonal hay fever was greatly improved after four to six days of such therapy in several patients, none of whom had responded to antihistamines.

Friedlaender and Friedlaender[54] studied three patients who were hospitalized with severe hay fever and responded favorably to ACTH given during the first few days of the season, with no active symptoms for the remainder of the ragweed season. Of sixteen patients who received 25 mg of ACTH daily for eight days on an ambulatory basis, fourteen did not receive any benefit. Five of their patients received cortisone injections for periods of seven to seventeen days; one was completely relieved, two markedly relieved, and two derived no benefit. Oral cortisone gave prompt relief to six of eight patients so treated. They noted several side effects from therapy. Forsham[53] made similar observations.

Koelsche and his co-workers[86,87] studied the effects of both hormones in nasal allergy and hay fever, in addition to other allergic diseases. They noted marked to moderate symptomatic relief in five of six cases of hay fever, the relief being confined to the period of administration, with recurrence two to three days after cessation of treatment. These authors feel that these drugs were possessed of no demonstrable curative value, but they do have a place in the symptomatic treatment of those patients who fail to respond to orthodox therapeutic measure.

The *J.A.M.A.*[114] in answer to a query concerning the use of cortisone and ACTH in children or adolescents suggests short periods of controlled usage only; however, these hormones are not substitutes for proper allergic management, either in adults or children. It is also noted that in acute allergic emergencies these drugs do not work rapidly enough to save a patient's life.

Untoward reactions to ACTH and cortisone are discussed by Derbes and Weiss,[37] with reference to the metabolic, electrolytic, and fluid balance, and androgenic and anabolic effects. Thromboembolic complications with ACTH and cortisone therapy were observed by Cosgriff.[29] Of 700 patients receiving therapy with these hormones, he noted forty episodes of thromboembolic complications in twenty-eight of the patients, and also observed hypercoagulability of the blood.

Jaros[83] presented an interesting hypothesis on the physiochemical pathogenesis of hypersensitivity. He presents the idea that such states are based on the imbalance between the catabolic phase, which produces tissue damage due to acetylcholine and histamine, and the anabolic phase, which concerns the secretion of enzyme-forming steroids from the adrenal cortex.

REVIEW OF BOOKS

A rather large number of books have appeared this year which include presentations on pollinosis at varying lengths.

To the pediatrically oriented allergist the book written by Chobot[24] should prove very interesting reading. This book is based on the author's

many years of pediatric allergy experience. The author frankly states his own opinions and supports them with illustrated case histories. The rôle of infection in the causation of asthma would not be agreed upon by many, but this is the view held by the author and many allergists.

Ratner's book[118] *Allergy in Relation to Pediatrics* is a compilation of discussions held in conjunction with a panel discussion of The American College of Allergists, with the assistance of members of the American Academy of Pediatrics. This book will acquaint physicians, whose primary interest is general pediatrics or general allergy, with the methods and results of those who are devoting a major portion of their efforts to pediatric allergy.

Two books devoted to clinical allergy have been published in English. Taub's[149] second edition of *Clinical Allergy* contains a considerable amount of new material. ACTH and cortisone are very well handled. The book is simple and practical, with the theoretical aspects less adequately covered. This book is a helpful guide for the beginner in allergy.

Davidson's[34] *Clinical Allergy* is dedicated to the thesis that "in allergy there is no immunity and that in immunity there is no allergy." While the author presents a highly controversial subject and is at wide variance with the views of most investigators, he doesn't offer any valid proof of his thesis. The practical portion of the book is more conservative in its view; however, many subjects discussed cannot be accepted by the writers.

Conn's[27] *Current Therapy 1951* contains an excellent section devoted to newer drugs used in allergy.

The most important books dealing with ACTH are those by Mote.[103] Volume I deals with all the research developments, and Volume II with the therapeutic uses of ACTH. There are many references relating to allergy in both volumes.

A fine book which should be read by everyone is the English translation of the classic *Serum Sickness* by von Pirquet and Schick.[160] Doctor Schick has succeeded in translating this into fluent English that retains the flavor of the orginal language. This book should be in everyone's library.

A number of books along popular lines dealing with allergy have been published. Alvarez'[4] *How to Live with Your Allergy* is the concept of the author but would not be accepted by all allergists. Swartz'[145] *Your Hay Fever and What to Do About It* is a practical book for the lay person. Herschfeld's[79] *The Whole Truth About Allergy* provides interesting reading. Feinberg's *Allergy: Facts and Fancies* should help the allergist when he is confronted by questions which sometimes prove difficult to answer.

Abramson's excellent book[2] *Somatic and Psychiatric Treatment of Asthma* is very worthwhile reading. This book has thirty-four individual contributors and contains much to be digested. There are many subjects which are of controversial nature, but this does not detract from the wealth of material dealing with the general subject of allergy.

Those interested in the relation of stress, the concept of the general adaptation syndrome and the adrenocorticotrophic hormone, et cetera, should read Selye's[132] *Annual Reports on Stress.*

An excellent textbook for the allergist interested in the fundamental principles of immunology is *Immunology* by Sherwood.[137] Another is Doerr's[39] *Die Anaphylaxie.*

An excellent textbook written in Italian is *Principi di Allergia Clinica* by Sangiorgi.[126]

La Pollinosi written in Italian by Serafini with Professors Gola and C.

Frugoni[62] as collaborators would be most welcome in an English edition. It is a very good book.

Several other books are reported but have not been reviewed. They are as follows: Swartz'[144] *L'allergie Traduit de L'anglais,* Tournoy and Vieville's[155] *Allergie et Traitement Sclerosant* and Whiteman's[164] *Bronchial Asthma. Its Relation to Upper Respiratory Tract Infections.*

The papers presented at the First International Congress of the International Association of Allergists appear in several issues of *Medecène & Hygiene.*[3,40,69,70,71,92,94,98,108,122,123,163]

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THE DYNAMICS OF THE IMMUNE RESPONSE

Of interest to allergists and immunologists will be a report of studies on the dynamics of immunity, by F. J. Dixon, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Results of studies by Dr. Dixon and his colleagues were presented before the recent meeting of the American Association for the Advancement of Science, at St. Louis. Dr. Dixon received $1000 and a bronze medal, the Theobold Smith Award in Medical Science, established in 1936 by the Eli Lilly Company. The award was granted for "demonstrated research in the field of the medical sciences, taking into consideration independence of thought and originality."

Dr. Dixon's studies cover a period of five years and are still very much in progress. He has aimed to devise the simplest possible immunologic system and subject it to a variety of experimental situations. The observations made on such a system may later be applied to the more complex but fundamentally similar immunologic processes in clinical medicine.

The first phase of this work concerned the distribution and catabolism of antigens in animals. The second phase concerned the antibody responses of laboratory animals to an assortment of labeled protein antigens. On the basis of the observations in the second series of experiments, it is possible to divide the immune response into an early radiosensitive phase and a later radioresistant phase. This brings the workers to certain conclusions concerning the role of various tissues in this process. Radiosensitive tissues, such as the lymphoid tissues, if involved in antibody production probably play their role in the early or adaptation phase. Certainly, the actual synthesis of gamma globulin molecules, or antibodies, does not appear to be dependent on radiosensitive tissues.

They also investigated another aspect of antibody response, which was the life span of antibody molecules. The life of the antibody molecules was measured in man and numerous animals, and was found to be inversely proportional to the metabolic rate of the species. In the human, the antibody half-life was two to three weeks, while in the mouse it was less than two days.

Dr. William Hammon employed these data on antibody life in the calculation of gamma globulin doses used for prophylaxis against polio in extensive field trials during the past two summers.

In Memoriam

LOUIS S. ROBINS, F.A.C.A.

We sadly announce the death of Dr. Louis S. Robins, F.A.C.A., of Chicago, Illinois, on January 8, 1953.

Dr. Robins was born in Russia, September 23, 1897, and was graduated from high school-gymnasium in Russia in 1914. He attended college at Northwestern University in Chicago and graduated in 1921 when he received degrees of B.S. and R.Ph. by examination. He graduated from Northwestern University Medical School in 1926 and interned at Michael Reese Hospital in Chicago, from May, 1925, to June, 1927. He served as Resident in Pediatrics from 1926 to 1928 and half-time at University of Illinois Medical School 1928-1931. He undertook postgraduate training in allergy as Clinical Pediatrics Representative in Allergy at the Research Hospital University of Illinois, 1929 to 1934. He associated in Pediatrics at University of Illinois Medical School from 1929 to 1942. He worked also in allergy at the Michael Reese Children's Clinic.

Dr. Robins resigned from his teaching position because of a progressive myasthenia gravis. Having been interested in Pediatric Allergy since 1928, Dr. Robins joined the American College of Allergists and participated in writing reviews for the ANNALS in the domain of Pediatric Allergy and Immunology. He also served on the editorial board. He was a member of the Cook County Medical Society, Illinois State Medical Society, and of the American Medical Association. He was a member of Alpha Omega Alpha honorary society. He was also a member of the Academy of Pediatrics, Chicago Pediatric Society and Chicago Medical Association. He published several medical articles before his retirement due to his serious illness.

Dr. Robins was beloved by all who knew him. In spite of his physical handicap, he managed to keep active in medical circles. He was an excellent pediatrician who recognized the importance of allergy and applied it to his practice. He was one of the best liked and respected pediatricians in Chicago. He was a hard, conscientious worker, conservative, intelligent, and well trained. In addition to his editorial duties, Dr. Robin participated in our Instructional Courses and helped whenever he could. We all deeply feel his loss.

Dr. Robins never married and in recent years lived a retired life at the Saranac Hotel, 5541 South Everett Avenue, Chicago, Illinois.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Sixth Annual Postgraduate Course on Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education of the American College of Chest Physicians and Laennec Society of Philadelphia, will be held at the Bellevue-Stratford Hotel in Philadelphia, March 23-27, 1953.

The 19th Annual Meeting of the College will be held at the Hotel New Yorker, New York City, May 28-31, 1953.

News Items

INTERNATIONAL COMMITTEE OF THE AMERICAN COLLEGE OF ALLERGISTS

Since its founding in 1942, The American College of Allergists has set forth the policy of promoting friendly intercourse and sincere relations with scientists throughout the world. Pursuant to this policy, the College, which has been honored by having its Chairman of the International Committee elected as the first President of the International Association of Allergology, announces the present appointments to the committee as follows:

Fred W. Wittich, M.D., *Chairman,* Minneapolis, Minnesota
O. Andrup, M.D., Oslo, Norway
Rudolf L. Baer, M.D., New York, New York
Leon Bentolila, M.D., Rosario, Argentina, S. A.
Jose A. Bozzola, M.D., Buenos Aires, Argentina, S. A.
C. J. C. Britton, M.D., London, England
Eduardo Canepa, M.D., Callao, Peru, S. A.
Arthur F. Coca, M.D., Oradell, New Jersey
Charles F. Code, M.D., Rochester, Minnesota
Cecil Collins-Williams, M.D., Toronto, Ontario, Canada
Fernando A. Cordero, M.D., Guatemala City, Guatemala, C. A.
Mario Damas Mora, M.D., Lisbon, Portugal
Hal M. Davison, M.D., Atlanta, Georgia
Mohan W. Dhurandhar, M.D., Bombay, India
E. Diaz Carrasco, M.D., Santiago, Chile, S. A.
Gösta Dohlman, M.D., Lund, Sweden
Isaac H. Erb, M.D., Toronto, Ontario, Canada
G. Estrada de la Riva, M.D., Havana, Cuba
Ulysses Fabiano Alves, M.D., Rio de Janeiro, Brazil, S. A.
Francisco J. Farrerons, M.D., Barcelona, Spain
J. Firket, M.D., Liége, Belgium
Arthur S. Grumbach, M.D., Zurich, Switzerland
M. J. Gutmann, M.D., Jerusalem, Israel
Bernard N. Halpern, M.D., Paris, France
K. Hansen, M.D., Lübeck, Germany
David Harley, M.D., London, England
Brian Henry Rowland Hill, M.D., Napier, New Zealand
Julian Roche Hunt, M.D., Balboa, Canal Zone
Paul Kallós, M.D., Helsingborg, Sweden
William Kaufman, M.D., Bridgeport, Connecticut
W. Kikuth, M.D., Düsseldorf, Germany
Luis A. Martinez Bula, M.D., Montevideo, Uruguay, S. A.
Hyman Miller, M.D., Beverly Hills, California
K. Nakamura, M.D., Osaka, Japan
Brum Negreiros, M.D., Rio de Janerio, Brazil, S. A.
Juan Nieves-Colon, M.D., Santurce, Puerto Rico
A. Oliveira Lima, M.D., Rio de Janeiro, Brazil, C. A.
David Ordman, M.D., Johannesburg, South Africa
Samuel Peck, M.D., New York, New York
M. Murray Peshkin, M.D., New York, New York
Bret Ratner, M.D., New York, New York
Bernard Riley, M.D., Sydney, Australia
Albert H. Rowe, M.D., Oakland, California
M. Salazar Mallén, M.D., Mexico, D. F., Mexico
M. Sanchez Medina, M.D., Bogota, Colombia, S. A.
Bela Schick, M.D., New York, New York
Louis Schwartz, M.D., Washington, D. C.
U. Serafini, M.D., Rome, Italy
Miguel Augustin Solari, M.D., Buenos Aires, Argentina, S. A.
Clarence Y. Sugihara, M.D., Honolulu, Hawaii
Leon Unger, M.D., Chicago, Illinois
W. J. Quarles van Ufford, M.D., Utrecht, Holland

AMERICAN ACADEMY OF ALLERGY—ANNUAL MEETING

The annual meeting of the American Academy of Allergy will be held Thursday, Friday and Saturday, February 26, 27 and 28, 1953, at the Hotel Statler, Boston, Massachusetts. Members of the College, particularly those residing in the East, should take advantage of the well-arranged program, and by their attendance at this meeting continue to demonstrate one of the ideals of the College: "to promote friendly intercourse and relationships between and among those engaged in the practice of allergy."

ARGENTINE SOCIETY OF ALLERGY

At a recent meeting of the Argentine Society of Allergy the following officers were elected:

President—Dr. León Bentolila
Vice President—Dr. J. F. Dumm
Secretary—Dr. H. Minsk
Assistant Secretary—Dr. J. Tamini
Treasurer—Dr. Martinez Marchetti
Assistant Treasurer—Dr. S. Wainfeld

Members of the Board of Directors are: Drs. L. Herraiz Ballestero, D. Kahn, Lopez Lacarrer, J. Aznarez, and Lorenzo Giscafré.

Dr. Bentolila is a Fellow of the College, Dr. Dumm is a Corresponding Member, and Drs. Herraiz Ballestero and Giscafré are Associate Members.

Dr. Bentolila, under a scholarship, attended the College Convention held in Chicago in 1951. He plans on being present to represent his society at the meeting of the American College of Allergists in Chicago next April.

SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will meet at the Hotel Muehlebach, Kansas City, Missouri, June 14-15-16, 1953. The sessions are devoted primarily to papers on practical aspects of allergy. Those interested in participating in the program are invited to write the president, Dr. Orval Withers, Bryant Building, Kansas City 6, Missouri.

Members of the local committee are Drs. Orval Withers, Cecil Kohn, R. Dale Dickson, Frederic Speer, Stanley Goldman, Ralph Hale, Herbert Rinkel, and Vernon C. Wiksten.

Reservations should be made early at the Muehlebach; they may be cancelled if unforeseen circumstances prevent attendance.

For information, write Frederic Speer, M.D., Secretary-Treasurer, 2601 Parallel Avenue, Kansas City 4, Kansas.

NEWS ABOUT ACA MEMBERS

Dr. Nelson Zivitz, F.A.C.A., announces the removal of his offices to Suite 318, One Lincoln Road Building, Miami Beach 39, Florida.

* * *

Dr. George Babcock, Jr., F.A.C.A., has been promoted to Assistant Director of Clinical Research of Schering Corporation, Bloomfield, New Jersey.

* * *

Dr. William Kaufman, F.A.C.A., has an article in the January, 1953, issue of *Coronet* entitled "Should Doctors Tell the Truth?" It is very thought-provoking.

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Recently the annual "Prize of Honor" for medical research workers from the "Vera and Carl Michaelsen Foundation" of the City of Helsingborg (Sweden) was awarded to Dr. Paul Kallós, Honorary Fellow of the College.

SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association will hold its next meeting at the Andrew Jackson Hotel, Nashville, Tennessee, May 15-16. For further information, please write the Secretary, Dr. Katharine Baylis MacInnis, 1515 Bull Street, Columbia, South Carolina.

CLINICAL SEMINARS ON PSYCHOSOMATIC ALLERGY

A questionnaire was sent by the Psychosomatic Committee of the College regarding psychosomatic factors in allergy. Four hundred thirty-three manifested an interest and seventeen indicated they had no special interest. This is rather a phenomenal response and stimulates the subcommittee to do their utmost to satisfy this need.

This enthusiasm warrants a large attendance at the evening clinical seminars on psychosomatic allergy, to be held in conjunction with the Ninth Annual Congress in Chicago, Sunday, April 26, 8:00 to 10:00 p.m., when emotional factors in allergy disorders will be informally discussed with demonstrations of actual procedures used in diagnosis and treatment, tape recordings of interviews with allergic patients, psychoanalytically oriented interviews and an actual interview with parents of an allergic child, and an actual diagnostic play session with an allergic child.

SECTION ON ALLERGY
MEDICAL SOCIETY OF THE COUNTY OF KINGS

The next regular meeting of the Section on Allergy of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn will be held at the Society Building on Thursday, March 12, 1953, at 9:00 p.m.

Program

"Allergic Manifestations in the Gastro-Intestinal Tract"

ALBERT F. R. ANDRESEN, M.D., Clinical Professor Emeritus of Medicine, State University of New York, College of Medicine at New York City

Discussors:

M. MURRAY PESHKIN, M.D., Consulting Allergist, Mt. Sinai Hospital, New York City. President-Elect, The American College of Allergists

MARY E. H. LOVELESS, M.D., Associate Professor of Medicine, Cornell University College of Medicine, New York City

ALLERGIST WANTED

WANTED: an allergist to associate with another allergist in the Pacific Coast area. Should be a young man certified or eligible for certification in internal medicine, and having a good background in allergy.

Please direct all inquiries to Assistant Managing Editor, ANNALS OF ALLERGY, 401 LaSalle Medical Building, Minneapolis 2, Minnesota.

BOOK REVIEWS

THE MANAGEMENT OF BRONCHIAL ASTHMA. Herbert G. J. Herxheimer, M.D., L.R.C.P. (Ed.), L.R.C.S. (Ed.). 107 pages. London: Butterworth & Co., Ltd., 1952. Price $3.45.

In attempting to write a guide to treatment in the management of bronchial asthma within the scope of approximately 100 pages, the author has been forced to omit much. Among other subjects, he does not discuss hyposensitization, hospital treatment, or prophylaxis. On the other hand, he gives a great deal of space to tests of vital capacity, although he omits voluntary ventilation capacity studies.

He feels that "if the history shows definite evidence of polyvalent allergy of the bronchi," skin tests are not necessary, but on the other hand feels that the patient can be tested by inhalation of the offending allergen, relieving the resultant bronchospasm by nebulized Isuprel or epinephrine.

He prefers large doses of Isuprel to those of epinephrine, and also uses ephedrine in much greater doses than those prescribed by American physicians. The details regarding the use of these drugs are, however, well worth reading.

The book is suitable for general practitioners rather than for allergists. It does not, however, give a balanced picture of the field, and when recommended to physicians, supplementary reading should be suggested. E. A. B.

A MANUAL OF CLINICAL ALLERGY. By John M. Sheldon, M.D., Professor of Internal Medicine, University of Michigan Medical School; Physician in Charge of University of Michigan Allergy Clinics; Robert G. Lovell, M.D., Instructor in Internal Medicine, University of Michigan Medical School; and Kenneth P. Mathews, M.D., Assistant Professor Internal Medicine, University of Michigan Medical School. 413 pages, 27 figures, 13 tables. Philadelphia and London: W. B. Saunders Company, 1953. Price $8.50.

This manual is divided into twenty chapters devoted mostly to detailed description of laboratory procedures, together with an adequate index. It presents the subject in a manner which has been found practical at the allergy clinics at the University of Michigan Hospital and the University of Michigan Health Service. It has developed from the training program provided for medical students and the postgraduate courses in allergy at the University Hospital.

To those allergists who are not familiar with the more recent literature and the constant additional syndromes which are either partially or wholly attributable to allergic cases, the book in some parts may appear disproportionate. However, the authors point out that it is necessary to delete lengthy discussions of differential diagnosis, immunologic theory and controversial matters. On the other hand, they have purposely laid undue stress on certain aspects of the practice of allergy which are not thoroughly covered in the more recent standard texts. Particular attention has been paid to the sections on pollen and mold identification and they clearly define preparation of extracts for testing and treatment.

The authors point out that the allergist must often make an extended search when seeking the allergenic offenders into such fields as otolaryngology, psychiatry, dermatology, neurology, chemistry, botany, and "even into other realms which may have little direct relationship to medicine." In the light of the growing appreciation of the importance of allergic diseases, and the qualifications for a competent allergist, the authors still use the worn-out statement that "there is need for more physicians who practice a good quality of allergy based on a sound medical background." Since allergy can involve any tissue or cell of the body and is correlated with all other specialties, it is no longer tenable to consider that the qualified allergist does not already possess a sound medical background. In actuality, the high standards set by those teaching allergy, as well as by those who have been disciplined and certified in the various specialties before becoming allergists, have acted to reverse such opinions. One of

the greatest obstacles to progress in the field of allergy at the present time is the certified young specialist well-trained in his own specialty but not in allergy. His armamentarium consists solely of drug therapy, or in some instances psychotherapy. He depreciates the essential immunization measures because he is not equipped with the type of laboratory material essential in the treatment of allergic conditions.

This manual stresses the importance of immunologic procedures and is an inspiration to those specialists in allergy to apply proper allergy diagnostic and laboratory procedures which are so essential in the management of an allergic patient. Until we appreciate the importance of allergy as a distinct and separate specialty, we shall have untrained practitioners and specialists to continue dabbling in allergy—who are known as "skin scratchers," and who are ignorant of the value of the diagnostic procedures necessary to make a proper diagnosis in allergy essential to its management.

ADVANCES IN INTERNAL MEDICINE. Volume V. Edited by William Dock, M.D., Long Island College of Medicine, Brooklyn; and I. Snapper, M.D., The Mount Sinai Hospital, New York. 464 pages. Chicago: The Year Book Publishers, Inc., 1952. Price $10.50.

There are nine chapters authored by various specialists in their respective fields. The chapters are: Diseases of the Pregnant Woman Affecting the Offspring, Catheterization of the Heart, Portal Hypertension and Its Treatment, The Anemia of Infection, Gout, a Derangement of Purine Metabolism, Clinical Aspects of Ganglionic and Adrenergic Blocking Agents, Aspects of the Influenza Problem, Experiences with ACTH and Cortisone, and Abnormal Proteins in Myeloma.

Each chapter has an extensive reference list. There are numerous figures and an author's index.

This last volume brings up to date some of the recent advances in internal medicine. There is no mention of the advances in our knowledge of Collagen diseases.